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MALIGNANT MONOBLASTOMA

A VARIANT OF MONOCYTIC LEUKEMIA *

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IN 1913 Reschad and Schilling-Torgau [1] reported the first case of monocytic leukemia to appear in the literature. Since then the disease has gradually gained recognition, and variations from its usual form, such as are found in association with other types of leukemia, have been observed. However, extensive tumor formation with primary multiple monoblastomata of the connective tissues ending in a terminal leukemic phase in which large numbers of primitive monoblasts flooded the peripheral circulation, such as is herewith described, has not previously been reported.

The acceptance of monocytic leukemia as a distinct disease has come through a recognition of the monocyte as an independent cell entity. The theory of cell relationship which advances this view is now generally accepted among hematologists, although other theories still find their adherents.

THE ORIGIN OF THE MONOCYTE

The method of formation of this cell has been one of the most controversial points in hematology. At least 19 different theories of the origin of the monocyte have been suggested [2]; of these the following have been given the widest recognition.

The unitarians (Maximow [3]) believe that the monocyte, in common with the other blood cells, takes its origin from the lymphocyte. All stages of transition from the small lymphocyte to the adult monocyte are described as occurring both in the circulating cells of the blood and among the resting cells of the tissues. They see in the lymphocyte an element which is relatively undifferentiated as to structure and function and which exists solely to produce other blood cells.

The dualists (Naegeli [4]) recognize two independent series of leukocytes. They believe that the monocyte is of myeloid origin, developing from the myeloblast, while the lymphocyte is an independent cell type.

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The generally accepted view today is that of the modified dualists (Cunningham, Sabin, and Doan [5]). These observers recognize three types of leukocytes, each with its own characteristic hematopoietic tissue, which arise from a common mesenchymal rest and stem cell. Just as the granulocytes normally come from myeloid tissue in the bone marrow and lymphocytes from lymphatic tissue in the lymph nodes, spleen, and diffuse lymphoid tissue of the body, so the monocyte arises in the connective tissue from so-called histiocytes of the reticulo-endothelial system. The development of the leukocytes of each series from a common stem cell is an irreversible process once the specific blast stage is reached. The structure and function of the reticulo-endothelial system is of particular interest in explaining the origin of the monocyte according to this theory.

The cells which compose the reticulo-endothelial system are probably as close to primitive embryonic mesenchyme as occurs in the adult body. They form the stroma of the lymphoid and myeloid tissue. In the stroma they occur as a reticulum whose cells flatten out to line the lymph and blood spaces where they are known as " endothelial " or " littoral " cells. In all diffuse connective tissues of the body they are found in close relation with fibrous tissue cells whose number they almost equal. Hereafter these connective tissue elements will be referred to as " tissue histiocytes." In the resting state they appear as dense elongated nuclei whose cytoplasm can not be identified. When activated they are large cells whose abundant cytoplasm is highly phagocytic. The morphological identity of the cells of this system is not always evident and they are primarily grouped on a functional basis. Their distinctive behavior is the storage of certain colloidal dyes when these dyes are injected into the body in a more dilute solution than can be taken up by any other cells of the organism. However, it is the function of hematopoiesis which is of immediate interest. Sabin, Doan, and Cunningham,[6] as a result of supravital studies, have described two types of wandering cells which take their origin from the reticulo-endothelial system: the clasmatocyte, or tissue macrophage, and the monocyte. They believe that the clasmatocyte takes its origin from the " endothelial " lining of the blood and lymph spaces. This is a large cell which is characteristically found in the tissue where it participates in local inflammation and takes up coarse débris, such as damaged red blood cells and products of tissue necrosis. The monocyte, which arises from the histiocyte of the diffuse connective tissues, is a smaller cell, also found in the connective tissues but maintained at a relatively constant level in the circulating blood. This cell is also phagocytic but takes up finer particulate matter than the clasmatocyte and has an affinity for lipoids. Other observers believe that these two cells, while morphologically and functionally distinct, represent two phases in the life cycle of a single cell type, and the results of tissue culture tend to confirm this view.

Case Report

A white male, aged 63, a railroad engineer by occupation, was first seen on April 1, 1932, when he complained of general weakness and persistent abdominal distention and discomfort. In the past he had always been in good health and had led an active life. About the first of December 1931 he noticed that he lacked his usual strength and energy. He first consulted a physician in March and at this time he was told that he was anemic. He noticed a slightly palpable, reddish eruption on the inside of the calf of each leg and the lower thigh. In addition to this a few small subcutaneous nodules were noted on the lower abdomen which later spread over the trunk, arms, and the region of the scalp. With the appearance of these nodules tenderness of both testicles was complained of. Up to the time that he presented himself for examination he had no relief from any of his symptoms and there had been a gradual increase in the number of subcutaneous nodules.

Examination: The patient was a man of small stature, of adipose muscular type. His height was 5 feet 4½ inches, weight 124 lbs., pulse rate 80, temperature 98° F., blood pressure 120 systolic and 70 diastolic. There was evidence of slight loss of weight. General nutrition was fairly good, although the skin and mucous membranes had a pale, pasty appearance. The gums were in good condition. The skin and mucosae were free from petechiae. There was a maculo-papular eruption of numerous dark red, more or less confluent lesions covering an area the size of the palm of the hand above and below the knee on the inside of each leg. Their color did not blanch on pressure and the eruption was evidently due to an intracutaneous infiltration. About 200 pea-sized, subcutaneous nodules were distributed over the trunk, arms, and upper third of the thighs. These nodules were firm, discrete, and freely movable in the subcutaneous fat, although a few of them were attached to the dermis. Where the nodules were attached, the surface of the skin had a reddish discoloration which could not be pressed out. Ten slightly larger, hemispherical nodules were adherent to the periosteum of the skull. The scalp was freely movable over these nodules. The face and forehead were free from lesions. The lymph nodes showed no significant adenopathy. The tonsils were small, irregular, and free from congestion. The liver and spleen were not enlarged either to percussion or palpation. There was a slight, uniform distention of the abdomen with diffuse tenderness on palpation. The prostate was normal in size and contour, and microscopic examination of its secretion was negative. Both testicles were normal in size, contour and consistency. There was a moderate, uniform, firm enlargement of each epididymis which was quite tender. The bones and joints were normal. Neurological examination was negative.

The patient was referred to a dentist who, after radiographic examination of all teeth, reported that there was no oral sepsis. Later an infected molar was found which was extracted. This was followed by slight oozing for 24 hours. The blood clotting time was three minutes.

Radiographic examination of the bones of the pelvis and lower spine was negative. The urine was essentially negative.

Treatment and progress: (Two subcutaneous nodules were removed for biopsy from the anterior chest wall on April 11). The injection of arsenic in the form of sodium cacodylate, gr. ¾, subcutaneously every second day was begun on April 4 and continued at this interval until July 8. There was a very striking improvement in the patient's symptoms after a few of these injections. He no longer suffered from abdominal discomfort and noticed a definite return of strength and energy. At the same time the maculo-papular eruption on the legs rapidly disappeared, leaving a brownish pigmentation of the skin. The subcutaneous nodules were reduced to not over 25 in number. Then, without any change in the subjective symptoms, the nodules increased rapidly in number until there were about 100 of them. At the same time

the testicles enlarged to twice their normal size, while the epididymi remained moderately enlarged as previously noted. The Aschheim-Zondek test was negative.

Radiation of the testicles and nodules was begun on May 10. As the result of one exposure each testicle and epididymis was reduced to a small, irregular, firm mass not over 2.5 cm. in its greatest diameter. The subcutaneous nodules which were directly radiated disappeared promptly, so that after 11 exposures to radium and roentgen-ray over a period of three weeks only 10 nodules were present. (On May

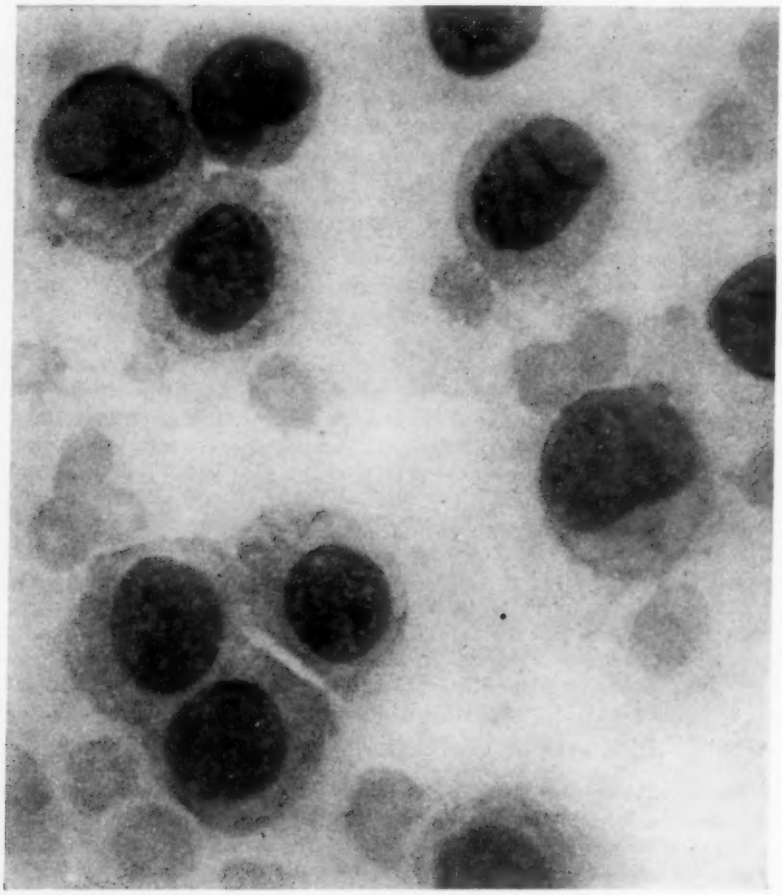


FIG. 1. Peripheral blood smear, Wright's Giemsa stain. × 900. *Monoblasts:* These cells have thin irregular borders. Their cytoplasm has a cloudy appearance and often contains innumerable dust-like azurophilic granules. Its staining reaction is moderately basophilic. The nuclei are eccentrically placed, and are round, oval, or bean-shaped.

15 two subcutaneous nodules, neither of which was directly radiated, were removed for a second biopsy.)

On July 8 it was noted that the number of nodules had increased definitely in spite of continued radiation and administration of arsenic. The patient complained of a return of general weakness. This marked the beginning of the final exacerbation of the disease. Abdominal discomfort and flatulence returned and persisted. Roentgenographic examination of the stomach and intestines showed no evidence of any

pathologic lesion. A chest roentgenogram at this time appeared essentially negative. On July 21 an elevation of temperature, varying around 101° F., was noted. This persisted without change up to the terminal hyperpyrexia. Demonstrable enlargement of the liver and spleen occurred during the final 10 days of the illness. The liver extended more than three fingers breadth below the costal margin and retained its normal contour. The spleen was just palpable at the costal margin. There was never any palpable enlargement of the lymph nodes. Shortly after enlargement of

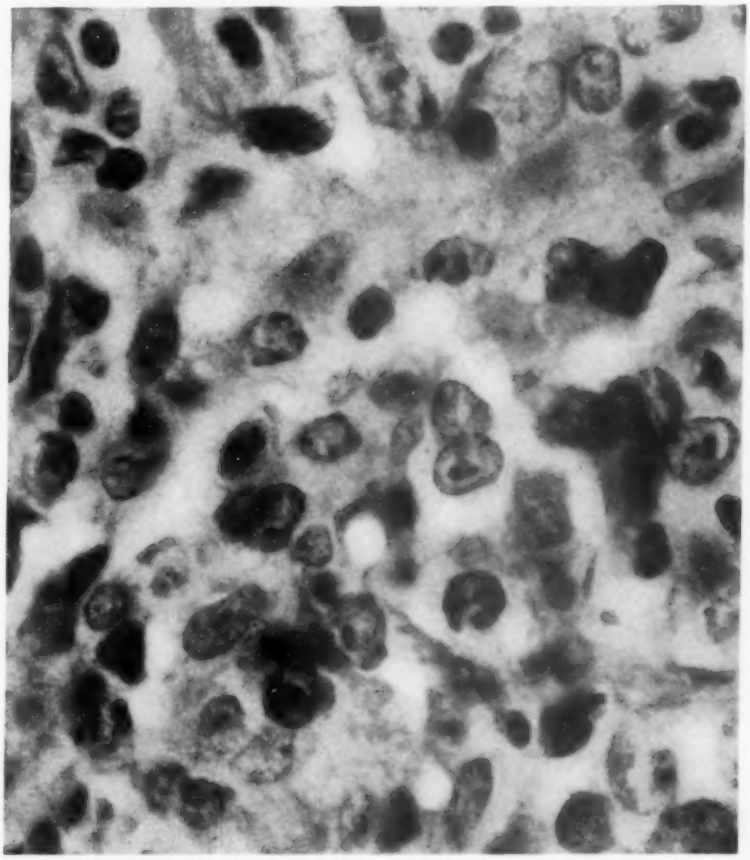


FIG. 2. Monoblastoma from subcutaneous tissues. Hematoxylin and eosin stain. × 900. The nodule is composed of large, blast-like cells with vesicular nuclei and an occasional prominent nucleolus. The cytoplasm of these cells appears to form a syncytium. A few small lymphocytes are present.

the liver and spleen was noted there was oozing of blood from the gums and repeated small hemorrhages of bright red blood from the bowels. Multiple small areas of submucous and subcutaneous hemorrhage also made their appearance. Administration of arsenic and irradiation were discontinued on July 8, but after this there was no striking increase in the number of nodules, although they individually grew to a slightly larger size. About two dozen were present at the time of death and the largest nodule measured 1.5 cm. in diameter. One nodule involved the periosteum of the lower end of the sternum. The leukemic blood picture was first noted on August 3. There was never any marked loss of body weight and no cachexia.

The behavior of the nodules during the course of the disease was interesting. The patient noticed no tendency for them to disappear spontaneously until treatment was begun. Their temporary response to the administration of arsenic was striking and they were very radiosensitive. There was a constant tendency for new nodules to appear even when the older ones were disappearing most rapidly under treatment. Their growth seemed to be under some degree of control, since they never increased

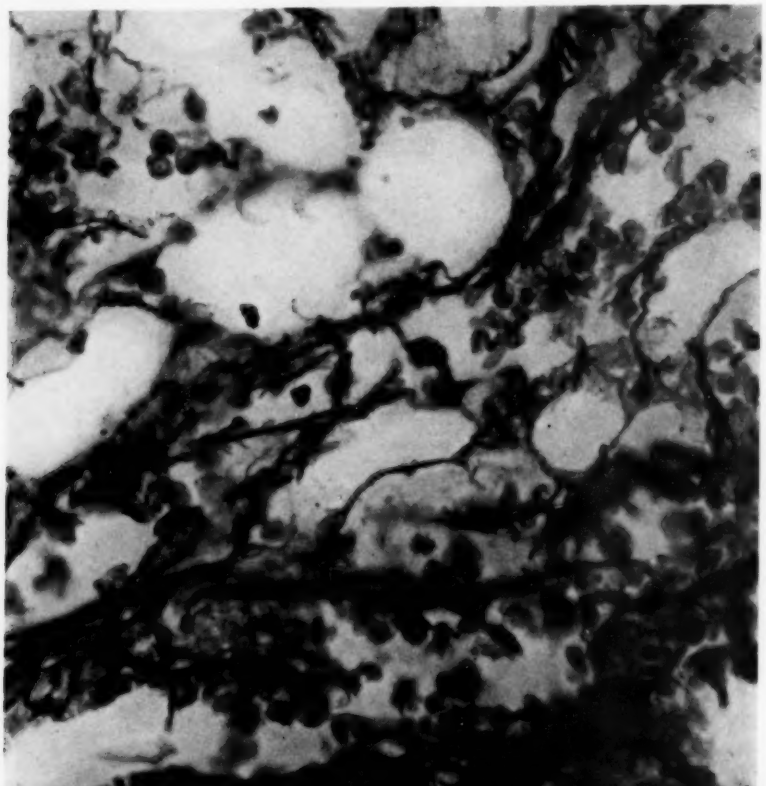


FIG. 3. Section from the periphery of the same nodule as figure 2. Foot's reticular stain. × 100. This section shows that the number of argyrophyl fibers present varies directly with the number of monoblasts in any part of the section.

greatly in size or infiltrated beyond the periosteum or subcutaneous fat in which they originated.

Examination of Tissue Removed at Biopsy. April 11, 1932. Two nodules were removed each of which was the size of a large pea. One shelled out from the surrounding fat with a smooth surface but showed no evidence of a capsule. The borders of the second nodule merged into the surrounding adipose tissue without any line of demarkation. The cut surface of both nodules was firm and elastic and pinkish-gray in color. The section stained with hematoxylin and eosin showed large blast-like cells infiltrating fat (figure 2). There was a moderate amount of cytoplasm but no cell outline could be made out. A few of the cells contained a little fine phagocytized material. They had large malignant looking vesicular nuclei which

were round, oval, or deeply indented and varied greatly in size. They often contained one nucleolus. Many cells contained mitotic figures. There were no giant cells present. There were a very few adult lymphocytes scattered throughout the section, and a very few collagen fibers were present. There was no evidence of hypervascularization of the tissue.

Sections of the nodules were referred to a number of pathologists. At this time the majority regarded the growth as malignant blastoma although the possibility of carcinoma and sarcoma was also suggested.

With Foot's reticular stain numerous fine argyrophyl fibers were demonstrated in the nodule. These fibers were more numerous toward the center of the nodule where the infiltrating cells were closely packed and they followed the cords of cells toward the periphery (figure 3).

May 13, 1932. Two subcutaneous nodules were removed. They were similar grossly and microscopically to the nodules described above.

Description of the Blood

Dr. C. A. Doan saw this patient in the different phases of his illness and Doan and Wiseman [10] have referred to the leukemic manifestations of the case in the report of a series of cases of monocytic leukemia which have come under their observation. The present detailed analysis of the case has been made in coöperation with these investigators and with their concurrence in the interpretations of biopsy and postmortem material.

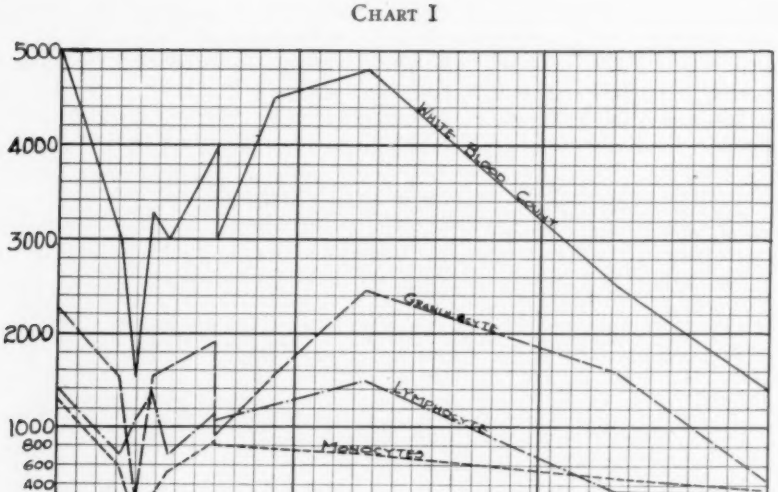
The differential counts were made from fixed smears with Wright's stain and by the supravital method.

The disease had two phases. The aleukemic phase lasted seven months after the onset. The onset of the leukemic phase probably coincided with the appearance of the terminal exacerbation of the disease three weeks before death, but was not demonstrated until one week before death.

In the aleukemic phase all of the leukocytes were mature. From the first there was a relative increase in monocytes in the blood with their absolute count normal or slightly reduced. (Table 1 (A).) The dramatic response of all of the leukocytes in the peripheral blood to the administration of arsenic was coincident with the rapid disappearance of the subcutaneous nodules, marked clinical improvement, and improvement in the anemia. (Chart I.) After two injections of sodium cacodylate there was a sharp reduction in the total number of granulocytes, the monocytes for a short time disappeared from the peripheral blood, while there was comparatively little change in the absolute number of lymphocytes. The administration of arsenic was continued but its effect on the blood picture was even more temporary than its effect on the nodules. There was a slight, rather uniform reduction in the number of all of the leukocytes when the subcutaneous nodules were dissolved by irradiation. At this time the monocytes were less affected than the cells of any other series. (Chart I.)

In the leukemic phase very primitive white blood cells, which were identified as monoblasts, dominated the blood picture. (Figure 1 and table 1 (B).) These cells varied in size from 12 to 30 micra and the average cell was large. The nuclei stained a reddish-purple with Wright's Giemsa stain. They occupied practically the entire cell in some cases, in others they constituted only a little over a third of the cell volume. The nuclei characteristically assumed an eccentric position. The cytoplasm had an opaque, bluish-grey appearance and was much darker in some cells than in others, due apparently to the increased amount of basophilic spongioplasm present. The cytoplasm of about one-half of the cells contained innumerable fine bluish-red granules. There was a varying number of small clear vacuoles present in some cells. A very occasional cell contained phagocytized material, which consisted either

CHART I



EFFECT OF THERAPY OF THE LEUKOCYTES OF THE PERIPHERAL BLOOD

Sodium cacodylate, gr. 3/4, was administered hypodermically during the entire period of time represented by the curves. In addition to this the subcutaneous nodules were radiated with radium and roentgen-ray beginning May 10. Coincident with the administration of arsenic there was marked clinical improvement and improvement in the anemia.

of coarse particles or degenerated erythrocytes. The cells were round or oval, usually very irregular in outline. Their borders were sometimes smooth but often were very uneven, due to numerous small protoplasmic projections which gave the edge an irregular, scalloped appearance. Occasionally there was a larger pseudopod-like projection. The nuclei were usually spheroidal or oval in shape and occasionally indented, while a few were irregular. The chromatin was arranged in a fine, skein-like network without pattern. One or two nucleoli were often present. In a few cells there was a bud-like projection of the nucleus. Degenerated nuclei, with or without protoplasm, constituted over 10 per cent of the cells. Non-nucleated cytoplasmic bodies of varying size were present. A few cells were undergoing amitotic division. Adult monocytes were very rarely seen and disappeared completely with the marked increase in the immaturity of all of the leukemic cells in the last count made 30 hours before death. The peroxidase reaction of these cells was not satisfactorily determined. A very few typical myelocytes were present. All lymphocytes were small and distinctly adult in type.

On supravital examination the predominating cell in the leukemic phase varied markedly in individual size. The cytoplasm was not clear, but had a mottled, greyish background in which was found a moderate number of fine bluish-green mitochondria. Many of these cells contained no neutral red vacuoles but those which did showed a typical arrangement about a clear area representing the centrosome, and were located just at one side of the nucleus. No motility was observed in any of the cells belonging to the monocytic series. No specific granules were present in any cells except those which were unquestionably myelocytes, of which there was a very minimal number.

A moderately severe secondary anemia persisted throughout the entire period. The red blood cells averaged seven micra in diameter. Occasional normoblasts were

TABLE I
A. Aleukemic Phase

TABLE I

A. Aleukemic Phase

Date, 1932	Hgb.	R. B. C.	Color Index	Reticulocytes	Erythrocyte Fragility	Platelets	Sedimentation Time, 1 hr.	W. B. C.	Differential								Total		
									Neut.	Lym.	Monocyte	Eos.	Base	Class	Myelocyte		Neut.	Lym.	Mono.
4–1	40	5						5,000	45	28	26		1				2,300	1,400	1,300
4–9								3,000	55	25	20		1				1,650	750	600
4–11	40	3.0				60,000		1,500	18	82	0						270	1,230	0
4–13	37	3.4		2%				3,300	46	45	8	1					1,518	1,485	264
4–15	40	3.1						3,000	52	24	19	1	1				1,560	720	570
4–21	42	3.7		2%	0.300	160,000	20 mm.	4,000	45	32	22	1					1,800	1,280	880
4–21	43	3.0	.66		0.369			3,000	30	40	28	2		2	2		900	1,200	840
4–28	55	3.3						4,500											
5–9	50	3.6						4,800	51	30	15	4					2,448	1,440	720
6–10	50	3.3						2,500	64	12	18	2					1,600	300	450
6–29	40	3.2						1,500	32	40	26	2					480	600	390

B. Leukemic Phase

Date, 1932	Hgb.	R. B. C.	Color Index	Reticulocytes	Erythrocyte Fragility	Platelets	Sedimentation Time	W. B. C.	Differential								Total			
									Lym.	Neut.	Eos.	Base	Monocyte	Monoblast	Myelocytes		Lym.	Neut.	Eos.	Base	Monocyte	Monoblast	Myelocytes
8-3	40	3.1			0.319–0.430			53,000	2	1			1	95	1		1,086	530	0	0	530	50,350	530
8-4						60,000		48,000	6	3			1	81	9		2,880	1,440	0	0	480	38,880	4,320
8-5	35	2.5	.77	.2%	0.341			76,000	3	3	2	2	3	86	1		2,280	2,280	1,520	2,280	2,280	65,360	760
					0.471																		
8-5		3.0		.6%		240,000		130,000	1	1			0	98	0		1,300	1,300	0	0	0	127,400	0

present. The erythrocyte fragility was normal throughout the aleukemic phase and increased in the leukemic phase. The blood platelets were decreased until the last, when they reached the normal range.

Autopsy

Permission was obtained for only a limited examination. There was a marked pallor of the skin and mucous membranes and a slight diffuse edema of the skin. Eight small areas of subcutaneous hemorrhage were scattered over the lower half of

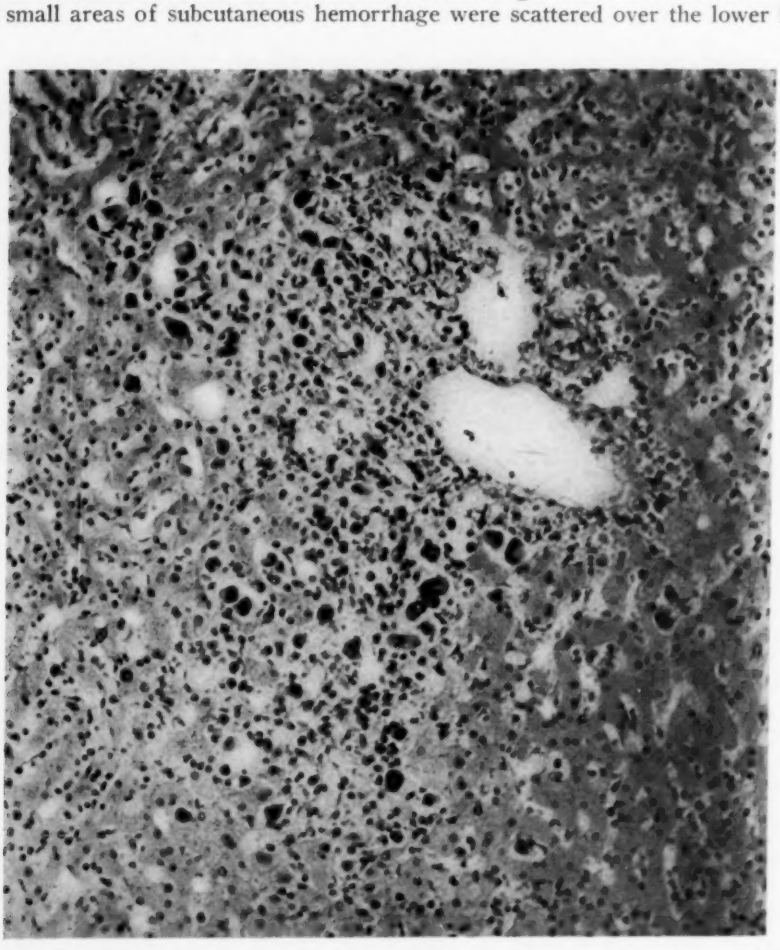


Fig. 4. Reticular hyperplasia in the liver. Hematoxylin and eosin stain. × 100. The reticular hyperplasia with many multinucleated giant cells completely replaces the liver cords in a small area at the periphery of a lobule.

the trunk and the thighs. Twenty-two subcutaneous nodules, varying in diameter from 0.5 to 1.3 cm., were present. One nodule was firmly attached to the periosteum of the sternum. There was no enlargement of the superficial lymph nodes. *Abdomen:* The peritoneum was normal. No mesenteric lymph nodes could be palpated. The liver was enlarged about 50 per cent, but retained its normal contour. It was uniformly firm in consistency. The cut surface had a mottled appearance due to a fine, golden-yellow trabeculation on a reddish-brown background. Three or four discrete, whitish, shot-like nodules were embedded in the substance of the liver. The

spleen was about three times the usual size and retained its usual contour. It was very soft and slightly uneven in consistency. The cut surface was dark red and came away very easily on scraping. Both kidneys and ureters, the right adrenal capsule, the pancreas, and the omentum showed no gross abnormality. A section was taken from the eighth and ninth ribs. Their medulla was red in color and firm in consistency. *Subcutaneous Nodule:* One nodule which was removed was roughly spherical in shape and measured 0.8 cm. in diameter. The borders merged into the surrounding fat without a definite line of demarkation. The cut surface of the central portion was firm, elastic, and pinkish-gray in color.

Microscopic Examination. Liver: The capsule was not thickened or infiltrated. The liver cords were thinned and the sinusoids were loosely packed with large mononuclear cells, giant cells, and often with swollen, partly desquamated endothelial cells. There was complete displacement of the hepatic tissue by reticular hyperplasia in areas of varying size (figure 4). Where these areas were small they occurred toward the periphery of the lobule; where they were large they completely displaced several lobules. They were composed of an imperfect reticulum whose stellate cells sent out broad protoplasmic processes often extending from one cell to another (figure 5).

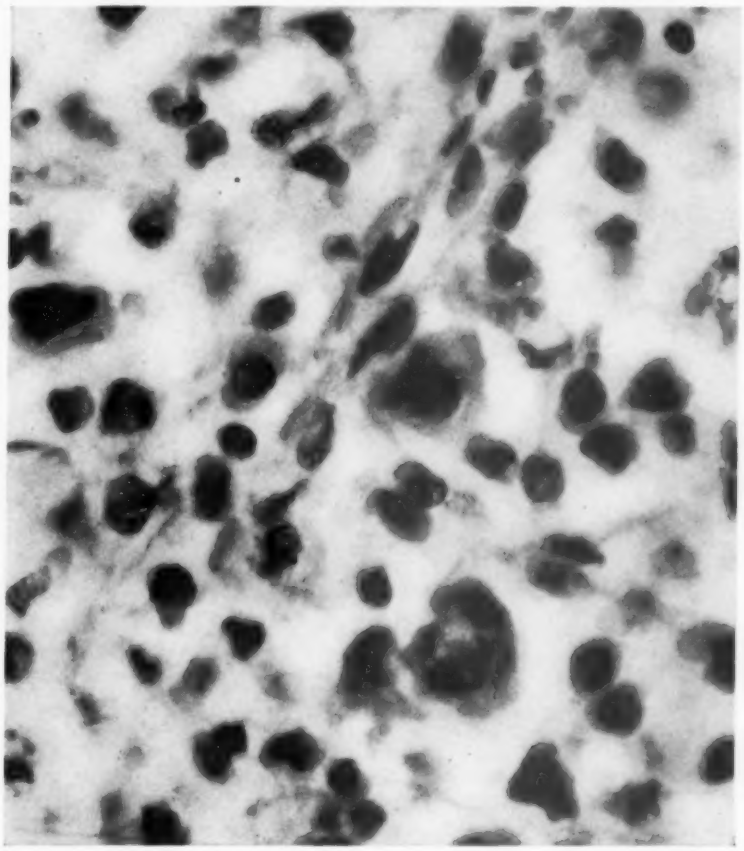


FIG. 5. Higher magnification of the reticular area shown in figure 4. Hematoxylin and eosin stain. × 900. The section shows an imperfect fragmentary reticulum formed by broad protoplasmic processes extending from one cell to another. Scattered throughout this reticulum are many free mononuclear and giant cells.

There was usually a background of amorphous intercellular substance. The cells of the reticulum usually contained one large vesicular nucleus, but occasionally up to five or six separate nuclei were included in a large protoplasmic mass. Many free mononuclear cells and multinucleated giant cells were scattered throughout this incomplete reticulum. These areas had a loose structure which was continuous at its margins, between gradually thinning liver cords, with the contents of the sinusoids. Mitotic figures were rarely seen in the free cells and never in the cells of the reticulum. Microscopically the shot-like areas mentioned in the gross were composed of closely

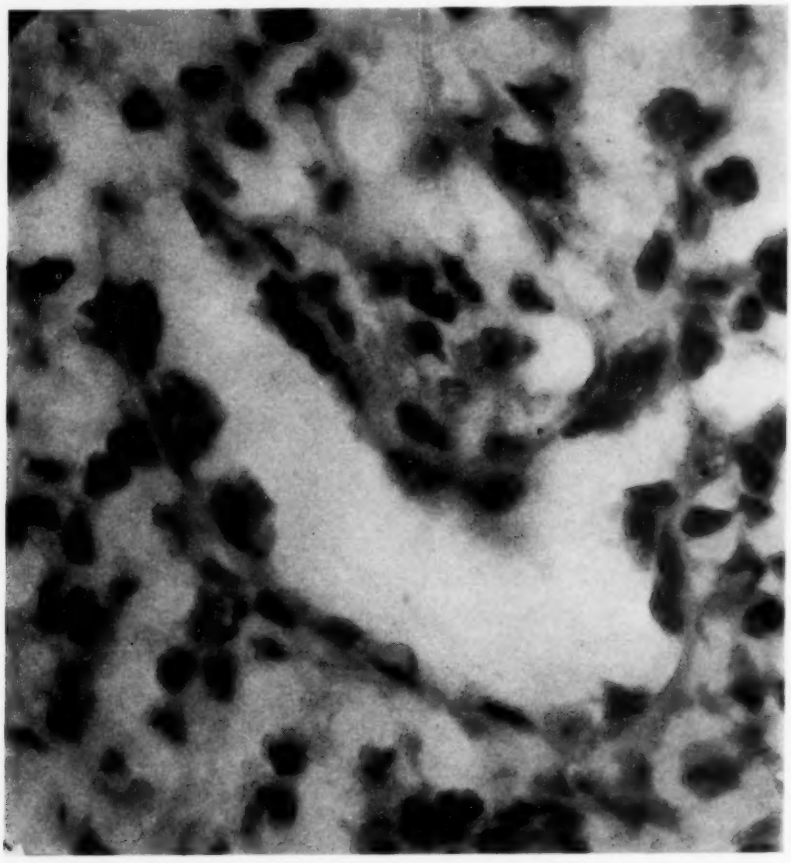


FIG. 6. Section of spleen. Hematoxylin and eosin stain. × 900. In the center of the figure there is a sinusoid cut longitudinally and surrounded by the loose reticular network of the red pulp. The lining endothelium of the sinusoid is swollen and apparently in the process of desquamating into the lumen.

packed mononuclear cells many of which were in mitosis. No suggestion of reticulum formation could be made out here, and giant cells were relatively infrequent. These nodules showed evidence of rapid expansile growth in that they compressed the surrounding liver cords into a pseudo-capsule at their periphery. With Foot's reticular stain the argyrophyl fibers, which outlined the liver cords, extended lightly but fairly uniformly throughout the reticular areas. Occasionally their course coincided with the broad reticular fibers previously described, but it was impossible to demonstrate any definite connection between the cells and these fibers, although a few cells showed a fine precipitation of silver in their cytoplasm.

Spleen: The capsule was not infiltrated or thickened. The normal architecture of the organ had disappeared. The white pulp of the Malpighian corpuscles was completely replaced by reticular hyperplasia which was essentially the same as described in the reticular areas of the liver. The sinusoids contained loosely packed mononuclear and giant cells with a minimal number of red blood cells. Their lining epithelial cells were sometimes normal but were often hyperplastic and definitely in the process of desquamating into the lumen (figure 6). Argyrophyl fibers, which were abundant in the blood vessel walls and in the fibrous framework of the organ, extended lightly and rather irregularly to all parts. The number of these fibers seemed to vary directly with the degree of reticular hyperplasia which was present in the different areas of the spleen.

Bone Marrow: The rib marrow only was examined with hematoxylin and eosin stain. No myeloid tissue was present. The medulla of the bone contained adipose tissue, which was extensively infiltrated by large mononuclear cells, a few of which were in mitosis. No giant cells were present (figure 7).

Kidney: There was very slight diffuse involvement of the interstitial tissues surrounding the tubules by mononuclear infiltration. This tissue also showed some evidence of hyperplasia by the presence of elongated spindle-shaped cells with vesicular

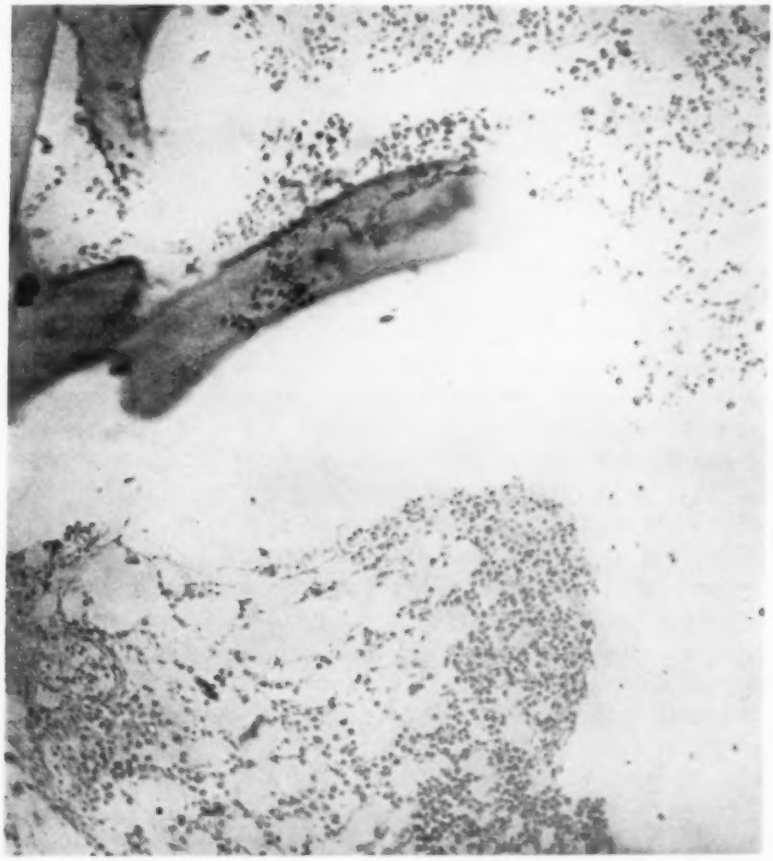


FIG. 7. Bone marrow. Hematoxylin and eosin stain. × 100. This shows a complete absence of myeloid tissue and a loose infiltration of medullary fat by large mononuclear cells.

nuclei. In addition to this there were areas of reticular hyperplasia with giant cells and mononuclear infiltration which displaced the surrounding tubules. In all glomeruli the cells lining the outer layer of Bowman's capsule were swollen.

Subcutaneous Nodules: The microscopic appearance was identical with that of the nodule removed at biopsy.

Omentum, striated muscle, pancreas, and fragments of fibrous and adipose tissue attached to sections of other organs were remarkably free from cellular infiltration.

The free mononuclear cells which infiltrated the spaces of the reticulum varied greatly in size having a diameter of from one and a half to four times that of a small lymphocyte. Their essential structure seemed to be similar to that of the cells of the reticulum and the monoblasts of the peripheral blood. The abundant cytoplasm was sometimes dense and took the acid stain, but more often was basophilic and stained lightly. A striking feature of these cells was that they were highly phagocytic for coarse débris. The cytoplasm was often vacuolated. The structure of the nuclei varied greatly; they were round, oval, or deeply indented. They were usually vesicular with one nucleolus, but were sometimes hyperchromatic. In sections stained with Wright's Giemsa, and Bailey's granular stain these cells showed no specific granules. *Multi-nucleated giant cells* were present only in sections of the liver, spleen, and kidney; that is, only in the organs where reticular hyperplasia was found. They did not occur in the blastomatous nodules or in the bone marrow. Some cells contained two nuclei and were slightly larger than the mononuclears; from these there were all variations up to very large cells with 10 or 12 discrete nuclei. They occasionally were seen dividing by mitosis with a very complex chromatin pattern in the manner of pure tumor giant cells.

Clinical and Pathological Characteristics of Monocytic Leukemia

Forty-two cases of monocytic leukemia from the literature have been reviewed. This probably represents little more than half of the total number which have been observed. Analysis of these cases shows this type of leukemia to possess the following characteristics. It occurred only in the white race and was definitely more frequent in the male than in the female. The youngest patient was five years and the oldest 71 years of age. The majority were adults. The onset in many cases was associated with an infection, either general or localized. Ulcerative stomatitis was frequently observed. This was often accompanied by a cellulitis and was far more extensive than is usually found with other types of leukemia. A moderate degree of fever was often present but was not a constant finding. Enlargement of the liver and spleen was frequently observed and when it did occur was usually of moderate degree, often first appearing late in the course of the disease. The lymph nodes were sometimes moderately enlarged but there was often no demonstrable adenopathy. There was universally a moderate to severe anemia of the secondary type. Platelets were either normal or reduced in number. There was a leukocytosis which usually varied between 5,000 and 200,000. The highest count exceeded 400,000 and aleukemic and subleukemic counts often occurred. The characteristic feature of the blood pictures was a relative increase in monocytes, varying from 50 to 96 per cent, averaging about 70 per cent of the leukocytes. The

majority of monocytes were characteristically immature. In monocytic leukemia a shift to the left often occurs in the other series of leukocytes. Immature cells of the myeloid series are present in the blood of many cases which remain essentially monocytic in type throughout their course. Such cells may constitute as high as 26 per cent of the total leukocyte count. When they reach a considerable number, areas of myelopoiesis may appear in the diffuse reticulo-endothelial hyperplasia.[7] A complete change of type from monocytic to myelogenous leukemia has been reported by Fontana [8] and by Kracke [9] (in a discussion of Foord's paper). Fontana also cites a case in which a change from myelogenous to monocytic leukemia was observed by Craciuneau and Calcalb. These are by no means the only instances in which change of type has been reported, but it is interesting to note that the change frequently follows a prolonged remission induced by radiation. The significance of these cases can not be evaluated until a greater number have been studied by uniform, modern, hematological technic. A shift toward immaturity in the lymphocytes, if present, is slight. The duration of the disease is usually from one to 10 months with a definite majority of the cases terminating in three months. Recently Doan and Wiseman [10] have made a valuable contribution to the conception of monocytic leukemia as a third, distinct type of leukemia by reporting the first case of this disease to run a distinctly chronic course.

Monocytic leukemia is always accompanied by characteristic pathologic changes in the fixed tissues. These consist of a hyperplasia of the reticulo-endothelial cells and differ only in detail from that described in the organs in the present case except that involvement of the lymph nodes, which is absent here, often occurs. This picture is usually readily differentiated from the other forms of hyperplasia of this system of cells such as are associated with faulty lipoid metabolism and with Hodgkin's disease. However, borderline cases do occur, and as has been pointed out by Marchal and Bargeton,[11] difficulty may be encountered in distinguishing monocytic leukemia from Hodgkin's disease on both clinical and pathological grounds. The same type of reticulo-endothelial hyperplasia which constitutes the pathological background for monocytic leukemia may occur and run a malignant course without any evidence of leukemia appearing in the peripheral blood.

Although monoblastomata in the diffuse connective tissues have not been described in connection with monocytic leukemia, Lasowsky [12] has reported an aleukemic case of malignant reticulo-endotheliosis with blastomatous nodules which may have been of this character.

Leukemic infiltration of the skin has been described in five cases.[1, 13, 14]

Discussion

This case comes under the classification of leukosarcoma and presents an aleukemic and a leukemic phase. There was an unusually widespread frankly malignant hyperplasia of reticulo-endothelial cells and the peculiar

feature of the pathologic change was multiple recurring monoblastomata which were formed by localized hyperplasia of the histiocytes of the diffuse connective tissues. In the aleukemic phase these nodules constituted the only involvement of the reticulo-endothelial system, while in the leukemic phase they were accompanied by hyperplasia of the reticulo-endothelial cells of the stroma of the organs. Since their occurrence antedated by at least five months both the leukemic blood picture and the clinical evidence of reticulo-endothelial hyperplasia in the liver and spleen, the nodules could not be explained either as localized deposits of circulating monoblasts or as tissue metastases.

The terminal leukemia was of pure monocytic type. Repeated examinations of the blood showed the great majority of the leukocytes to be monoblasts. And except for one count where there were 9 per cent myeloblasts, immature cells of the other leukocytic series were practically absent. In the spleen and bone marrow lymphoid and myeloid tissue were replaced by an overwhelming reticulo-endotheliosis.

Compared with the other hematopoietic tissues monoblastic tissue varies greatly in character and is unusually widely distributed throughout the body, so it may be expected to produce a more complex disease syndrome. However, the course of events in the present case finds a close parallel in a disease of the lymphatic system—malignant lymphoblastoma with terminal lymphatic leukemia. In both there is a characteristic type of malignant blastoma whose spread is usually limited to the tissues in which it originates, and the possibility at least of a terminal leukemia which reflects the character of the cells forming the blastoma.

Conclusions

1. Review of the literature and the study of the present case tend to substantiate the view that the monocyte has a separate origin from other leukocytes and that monocytic leukemia is a distinct disease.

2. A variant of monocytic leukemia, malignant monoblastoma with a terminal blood picture of monocytic leukemia, is described for the first time.

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CLINICAL STUDIES IN ELECTROCARDIOGRAPHY

III. PERSISTENT ABNORMAL LEAD IV FINDINGS IN SERIAL ELECTROCARDIOGRAMS, WITH NEGATIVE THREE ROUTINE LEADS, IN CORONARY THROMBOSIS *

By A. Allen Goldbloom, M.D., F.A.C.P., *New York, N. Y.*

In a previous publication [1] we presented a clinical evaluation of routine chest leads in cases of chronic coronary artery disease and acute coronary occlusion, with the findings in a series of 86 patients in whom, in addition to the three routine leads, a Lead IV tracing had been made. Of this series, 25 were normal controls, 40 were cases of chronic coronary artery disease and myocardial damage, 13 were cases of acute coronary thrombosis, and 8 were non-coronary cardiac cases. Of the 40 cases with myocardial damage due to chronic coronary artery disease, 25 showed positive findings in the three routine leads and a negative Lead IV; 12 showed positive findings in the three routine leads and a positive Lead IV; and three cases showed negative findings in the three routine leads and an abnormal Lead IV. Of the 13 cases of acute coronary thrombosis, four showed an abnormal Lead IV in the presence of negative findings in the three routine leads.

In order to determine whether or not there is persistence of abnormal findings in Lead IV, the four cases last mentioned were studied by serial electrocardiography and the findings were as follows:

Case I

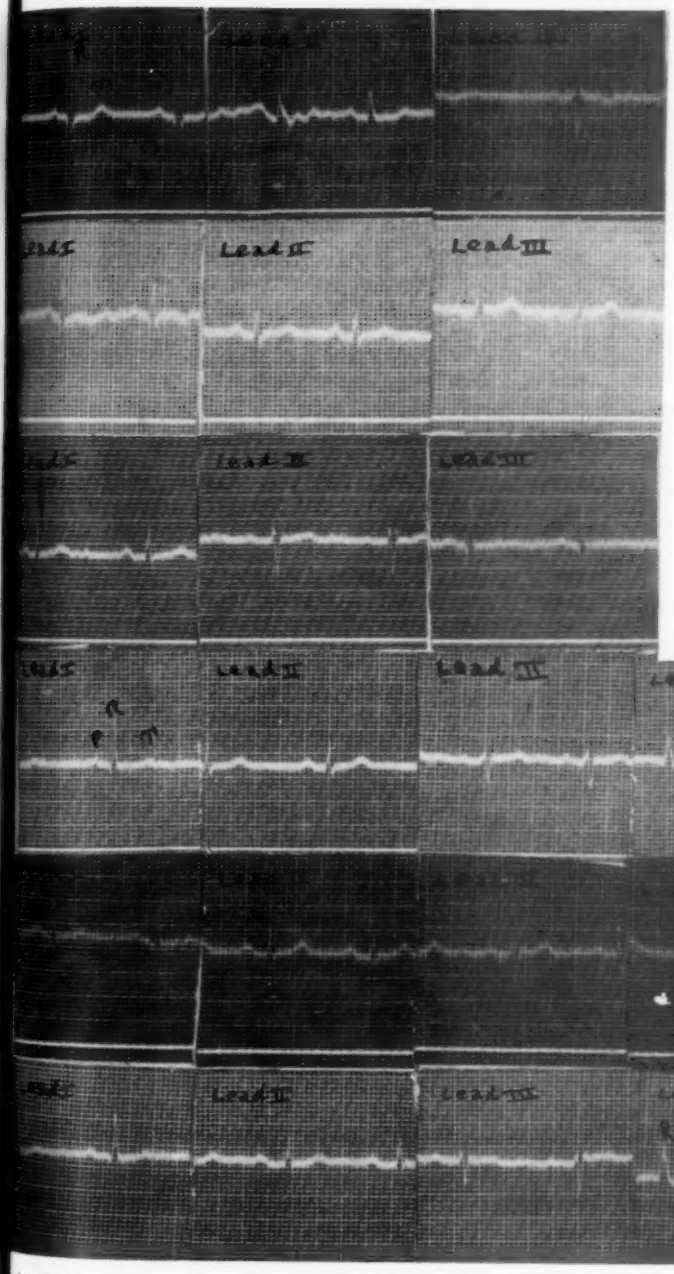
This patient, a man 53 years of age, became acutely ill August 23, 1932, with marked precordial pain radiating to the left shoulder and arm. There was no vomiting. He was seen at home on that day and an electrocardiogram was made at the bedside. It showed the T-wave inverted in Lead I, and diphasic in Lead II; in Lead III the complexes were inverted, suggestive of myocardial damage. Lead IV was not done at that time. A second electrocardiographic examination was made at the bedside next morning (figure 1, A), and showed: T_1 diphasic; T_2 poor; T_3 slightly above the isoelectric line. Lead IV tracing was not made.

The patient was admitted to the hospital August 24, and physical examination revealed the following: a very feeble pulse, weak and rapid heart sounds, cold perspiration and other signs of peripheral circulatory failure. There was a pericardial friction rub. The blood pressure was systolic 120, diastolic 80. The abdomen was markedly distended. The patient remained in the hospital two months, during which time several electrocardiograms were made which showed no change.

November 5, 1932, the patient came to the office as an ambulatory case and electrocardiographic tracing at that time (figure 1, B) showed only an inverted T-wave in Leads I and II.

On December 16, 1932, another electrocardiographic examination was made in the office (figure 1, C) which showed that the inverted T-wave in Lead I had become upright, was unchanged in Lead II, and was poorly visualized in Lead III.

* Received for publication May 22, 1934.



A, Aug. 24, 1932

B, Nov. 5, 1932

C, Dec. 16, 1932

D, Feb. 13, 1933

E, June 8, 1933

F, Oct. 23, 1933

1. Serial electrocardiograms showing persistently abnormal Lead IV, while the routine three leads are normal.

At the next examination, February 13, 1933, it was decided that a Lead IV tracing might be of aid inasmuch as there had as yet been no conclusive cardiographic evidence of coronary thrombosis. The findings (figure 1, D) were as follows: No evidence was seen in Leads I, II and III of myocardial damage, but Lead IV proved to be abnormal in that the Q-wave was absent, the QRS complexes were markedly slurred, and the T-wave was poorly visualized and diphasic. In other words, Lead IV definitely indicated myocardial damage due to coronary disease.

On June 8, 1933, a sixth tracing (figure 1, E) and on October 23 a seventh (figure 1, F) were made and both presented the same findings as in the February examination. There was no suggestion of coronary disease, except in Lead IV, which was persistently abnormal in both examinations.

The patient is still experiencing precordial pain and dyspnea on slight exertion.

Case II

The patient, a man of 41 years, experienced his first attack after midnight on November 10, 1932, suffering markedly severe precordial pain that radiated to the back and to the left shoulder, cold perspiration, extreme weakness, and vomiting. When seen by his family physician, Dr. M. H. Miller, the collapse manifestations had subsided somewhat, but there was a pericardial friction rub, marked tachycardia and gallop rhythm, with the slightest cough causing pain. There was less vomiting but the epigastric distress continued. The abdomen was distended. The blood pressure was systolic 120, diastolic 70. The patient had experienced mild precordial and substernal pain while driving a car eight months before, but this pain had subsided so quickly that he did not consult a physician.

November 11, 1932, an electrocardiogram taken at the bedside showed cove T-waves in Leads I and II. In Lead III the T-wave began below the isoelectric line. Lead IV was not taken. The clinical diagnosis was left coronary thrombosis. The patient remained in bed for six weeks, during which time serial electrocardiographic examinations revealed the following:

November 24, 1932: The cove T-wave in Lead I had receded until it was only an inverted T-wave; T_2 remained coved; T_3 began above the isoelectric line. Lead IV was not done.

December 13, 1932 (figure 2, B): T_1 and T_2 inverted; Lead III normal. Lead IV was abnormal in that there was an absent Q-wave, marked slurring of the QRS complexes, and the T-waves were directed upward.

December 28, 1932 (figure 2, C): Same findings as at last examination; Lead IV persistently abnormal.

January 14, 1933 (figure 2, D): Findings unchanged; Lead IV persistently abnormal.

March 15, 1933 (figure 2, E): No abnormality in the three routine leads other than an inverted T-wave in Lead I, insufficient to indicate myocardial damage. Lead IV, however, continued to show an absence of the Q-wave, marked slurring of the QRS complexes, and upward directed T-wave.

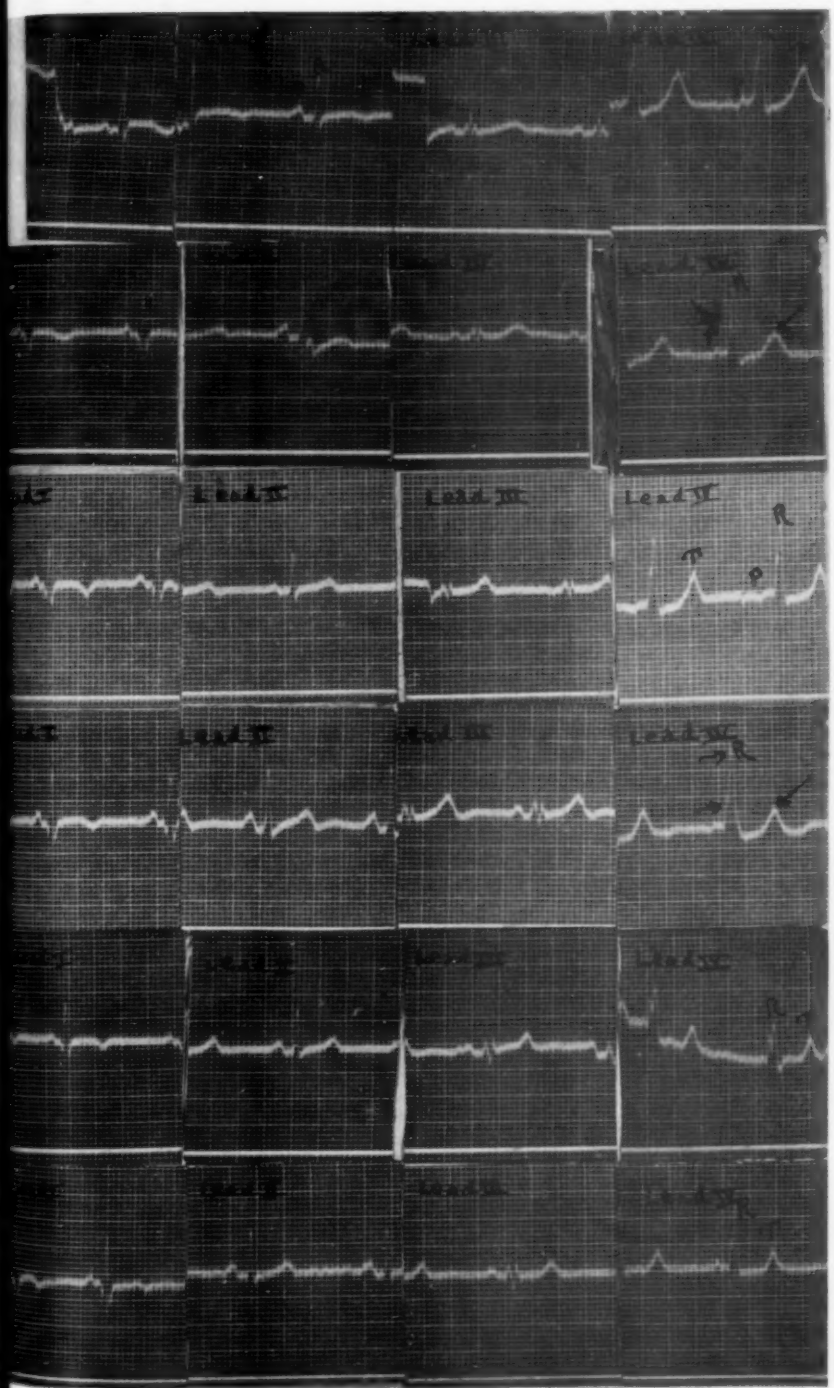
June 1, 1933 (figure 2, F): Findings unchanged.

December 10, 1933 (figure 2, G): Findings unchanged.

The patient has been without subjective complaints except those at the time of the acute attack.

Case III

A week before onset, the patient, a man of 52 years, complained of a foul, burning sensation in the throat, and marked belching. On January 12, 1933, he was awakened from sleep by severe pain over the entire sternal region. When seen, he was markedly ill, but without collapse manifestations except diffuse cold perspiration.



B, Dec. 13, 1932

C, Dec. 28, 1932

D, Jan. 14, 1933

E, March 15, 1933

F, June 1, 1933

G, Dec. 10, 1933

2. Serial electrocardiograms showing a persistently abnormal Lead IV, while the routine three leads show no characteristic changes of myocardial damage.

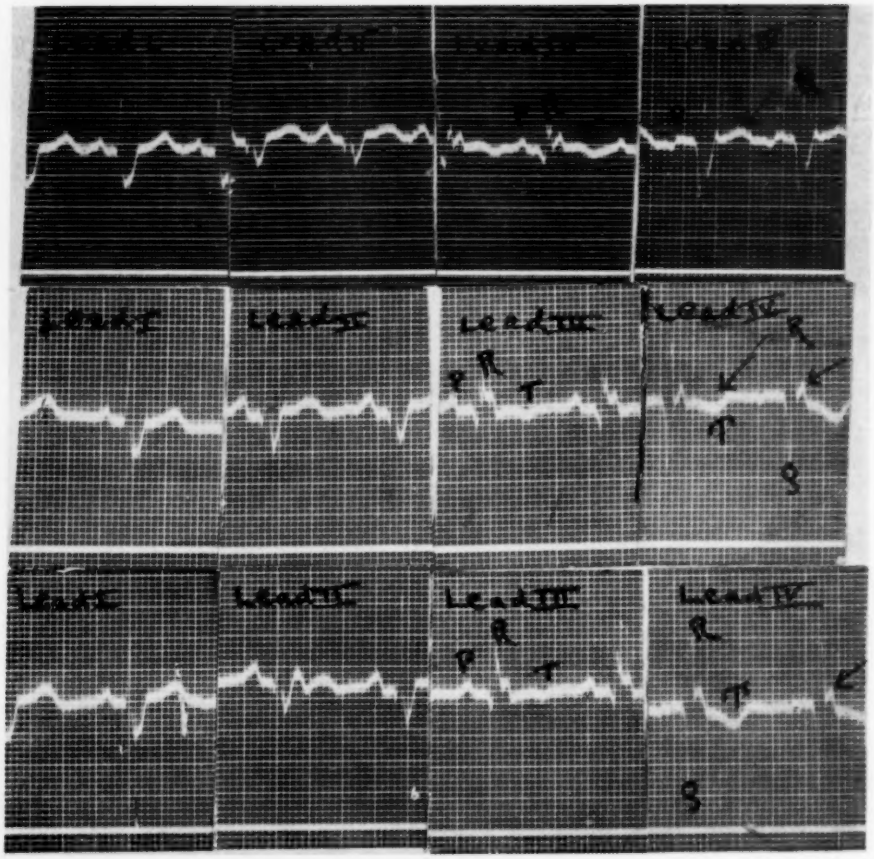


FIG. 3. Serial electrocardiograms showing persistently abnormal Lead IV, with the routine three leads suggestive of myocardial involvement.

His heart was rapid but regular, with a gallop rhythm. The pulmonic second sound was accentuated. The blood pressure was systolic 150, diastolic 100.

January 19, 1933, an electrocardiogram (figure 3, A) was made at the office. The QRS complexes were widened in Leads I and II and there were diphasic T-waves in these leads. Lead III was normal. Lead IV confirmed the diagnosis of myocardial damage in that it presented a slurred QRS complex and a T-wave beginning above the isoelectric line.

July 13, 1933: the patient was still dyspneic, experiencing precordial pain on exertion. Physical examination revealed a gallop rhythm. The aortic second sound was accentuated. The blood pressure was 130 systolic and 90 diastolic. Fluoroscopic examination showed that the left border of the heart extended beyond the nipple line and that there was a widened aorta. Electrocardiographic tracing (figure 3, B) showed only one abnormality in the three routine leads, namely a diphasic T-wave in Leads I and II. Lead IV was persistently abnormal as at the previous examination.

April 11, 1934: The electrocardiographic findings (figure 3, C) were unchanged from the last examination. The original subjective complaints were still present.

Case IV

While at work June 21, 1933, the patient, a man of 62 years, was suddenly seized with excruciating pain over the chest, radiating to the back and causing him to collapse. He was examined one hour later at Beth Israel Hospital, private service of Dr. I. W. Held, and was found to be in peripheral circulatory failure with clinical evidence of collapse. The heart sounds were faint and fetal in character, with a rate of 48. The blood pressure was 80 systolic and 50 diastolic. The abdomen was markedly distended. The liver was palpable. Electrocardiogram (figure 4, A) showed a normal Lead I, and cove T-waves in Leads II and III, evidence of right coronary thrombosis. Lead IV was not done.

On June 24, 1933, a second cardiographic tracing (figure 4, B) was made. Lead I was normal; the cove T_2 had become an inverted T_2, and cove T_3 had become upright. Lead IV was abnormal in that there was an absence of the Q-wave and marked slurring of the QRS complexes. The patient was still very ill and the physical findings of the heart were unchanged from the previous examination.

On July 12, 1933, while still in the hospital, the patient developed severe pain over the splenic area which was diagnosed as perisplenitis due to splenic infarction. Electrocardiographic examination (figure 4, C) showed an unchanged Lead I, the T-wave less inverted in Leads II and III, and a persistently abnormal Lead IV, with the T-wave even more markedly downward directed.

On July 26, 1933, the patient, subjectively much improved, came to the office and another electrocardiographic tracing (figure 4, D) was made. It showed a normal Lead I, inverted T-wave in Leads II and III, and a persistence of the abnormal findings in Lead IV as at the previous examination. On August 28, 1933, the electrocardiographic findings (figure 4, E) were unchanged.

Discussion

From the findings in the four cases reported above it is apparent that whereas the three routine leads returned to normal or almost to normal soon after the acute attack, Lead IV continued to show abnormalities, coinciding with the continuance of certain subjective symptoms in three of the cases. Without this persistence of the abnormal findings in Lead IV there would have been no electrocardiographic evidence of the fact that the patients'

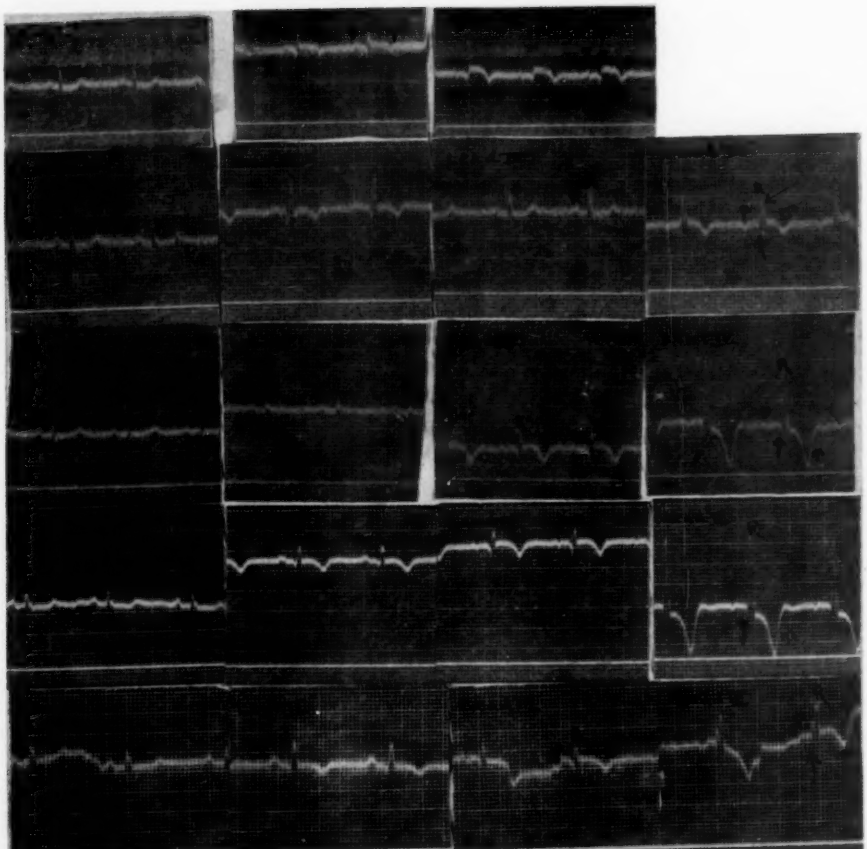


FIG. 4. Serial electrocardiograms showing persistently abnormal Lead IV. The routine three leads show evidence of myocardial damage.

recovery from their myocardial damage was still incomplete. This is of particular importance because the management of these cases depends upon the degree of myocardial damage.

There is no valid explanation of the abnormality of Lead IV. There are authors who claim that an abnormal Lead IV has not as much diagnostic significance as have abnormalities in the three routine leads, but one may say, also, that abnormalities in the three routine leads are not always positive evidence of coronary occlusion, but may be due to myocardial damage secondary to hypertension, renal disease, or decompensated cor-pulmonum, as demonstrated by autopsy findings.[2]

It is possible that the abnormality of Lead IV is, also, not always indicative of coronary occlusion. We have seen this recently in a case on the service of Dr. M. A. Rothschild, which showed a persistently abnormal Lead IV which at autopsy proved to have been caused by circulatory failure as a result of thromboangiitis of the smallest pulmonary vessels. The actual cause of the abnormality in Lead IV was probably anoxemia, as analysis of the patient's blood showed only 50 per cent of oxygen saturation. It has been shown experimentally by Keefer and Resnik [3] and more recently by Rothschild and Kissin [4] that anoxemia is a factor in producing the anginal syndrome. One must exercise caution therefore in interpreting abnormal Lead IV findings as directly due to coronary thrombosis with myocardial damage. In the four cases reported, the abnormal findings in Lead IV could not have been the result of anoxemia, however, for the reason that the serial electrocardiographic Lead IV tracings were not made in the acute stage, but after the subsidence of the acute attack. From the standpoint of prognosis, it is believed that further studies of the persistency of abnormal findings in Lead IV will provide criteria by which to judge expectancy of life.

Summary

In order to determine the persistency of abnormal findings in Lead IV, four cases of coronary thrombosis were studied by serial electrocardiography, following the subsidence of the acute attack, and the findings reported. In two cases, the three routine leads returned to normal within a short period of time; in the remaining two cases, there was a modification of the early abnormalities in these leads, to a degree that they were no longer positively indicative of myocardial damage. In all four cases, the only abnormal electrocardiographic findings that have persisted, showing the incomplete recovery of the patients from their myocardial damage, are those in Lead IV.

Conclusions

Abnormal Lead IV findings persisted in four cases of coronary occlusion. This was not the case with the abnormalities in the three routine leads. Without the Lead IV serial tracings, therefore, one could not have been certain electrocardiographically that the patients were still not fully re-

covered from their myocardial damage. Hence we recommend that serial Lead IV tracings be made in cases of coronary thrombosis, not only for their diagnostic value but particularly to serve as a guide in treatment and management.

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CAROTID SINUS REFLEX HYPERSENSITIVITY *

By Henry Monroe Moses, A.M., M.D., F.A.C.P., and Sol S. Feinstein, B.S., M.D., *Brooklyn, N. Y.*

It is not unusual to see patients who present symptoms of fainting, nausea, vomiting and convulsions without the presence on examination of any obvious pathological condition which might explain these attacks. The relation of disturbances of the function of the carotid sinus to the appearance of such symptoms has been not infrequently noted in the recent literature,[1, 2] but our knowledge of the clinical phenomena in such cases is still fragmentary. It seems timely therefore to report certain observations made in two patients on the writers' service at the Kings County Hospital.

Case Reports

Case 1. A 45 year old Italian laborer, admitted to the Kings County Hospital, complained that three hours prior to admission, on arising, for no apparent reason he suddenly developed dizziness, faintness, headache, vomiting, and a generalized convulsive seizure which recurred three times at 15 minute intervals. He then recovered consciousness and, except for a headache, felt perfectly well when brought to the hospital. His family history, as well as his past personal history, was negative. Physical examination showed a robust individual of medium height with no abnormal findings except carious teeth. The blood pressure was systolic 142, diastolic 84. The

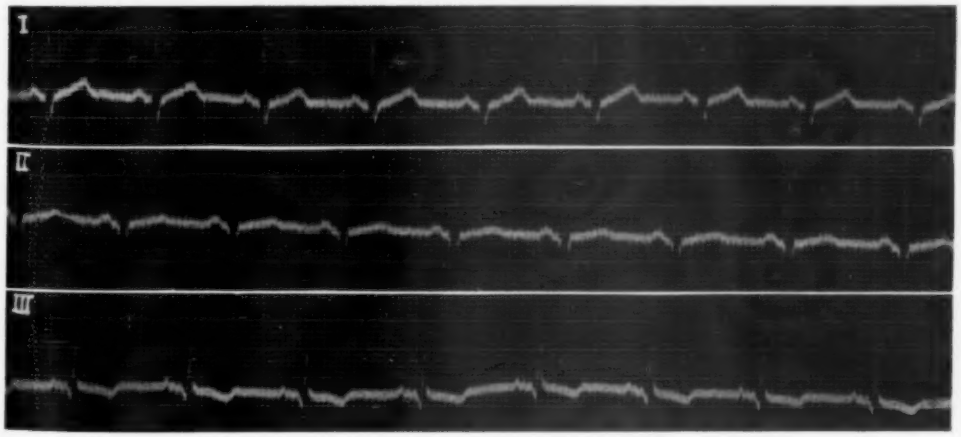

Fig. 1. Patient's normal electrocardiogram, Leads I, II and III. Rate 80. P–R interval, 0.12 sec. Lead III shows slurring of R and notching of P suggestive of some myocardial damage.

urine was normal. The blood chemistry examination showed: urea, 29 mg. per 100 c.c. of blood; creatinine, 1.2 mg.; sugar, 133 mg. The blood count was: red blood cells, 3,850,000; hemoglobin, 70 per cent; white blood cells, 9,250; polymorphonuclear

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From the Medical Service, Kings County Hospital, Brooklyn, N. Y.

FIG. 2. Electrocardiogram during maintenance of pressure over right carotid sinus. Heart stopped completely at *A* and remained stopped for eight seconds except for one idioventricular beat at *B*.

neutrophiles, 78 per cent. The blood and spinal fluid Wassermann examinations were negative. A roentgen-ray of the skull showed no abnormalities.

On careful reëxamination of the patient, it was noted that the bulb of the right carotid sinus was more prominent than that of the left. Figure 1 shows an electrocardiographic tracing of this patient in his normal condition. Pressure on the right carotid sinus produced promptly a more and more marked slowing of the heart rate, until finally the heart stopped for eight seconds as shown in figure 2. The patient developed congestion of the face; the eyes turned upward and inward; the breathing became deeper and stertorous; profuse perspiration appeared; unconsciousness developed and in a few moments he suffered a generalized clonic convulsion. Both subjectively and objectively the convulsive seizure seemed to be identical with the seizure at home. Following this episode the patient complained of headache with nausea but recovered after one hour.

Electrocardiographic studies of this reaction were made which showed a gradual slowing of the sinus rate with no evidence of any change in the auriculo-ventricular conduction time. Cessation of cardiac pulsation for eight seconds took place, at the

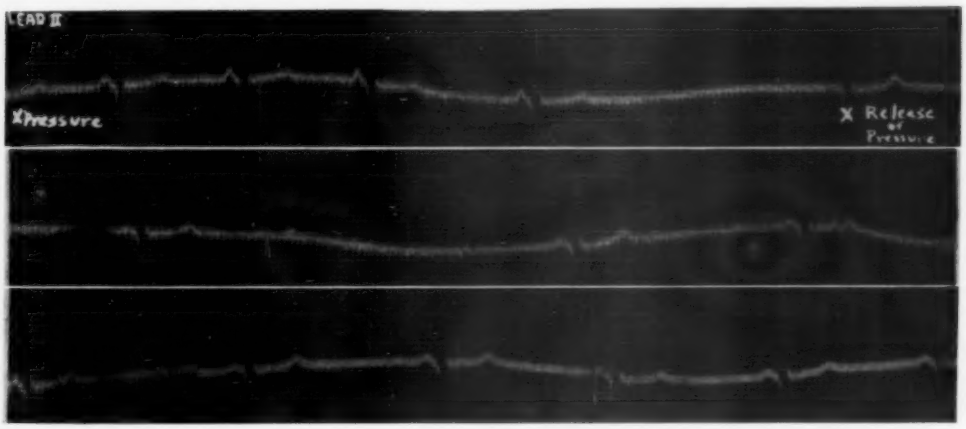

FIG. 3. Electrocardiogram showing effect of pressure over right carotid sinus; pressure was released as soon as heart slowed.

end of which time the patient had a convulsion. The electrocardiogram showed one idioventricular beat at the end of three seconds. In this first study, pressure was maintained until the patient had a convulsion. In later studies, pressure was maintained only until the patient showed clinically signs of loss of consciousness. Pressure was discontinued, however, before convulsions began. A certain degree of quantitative correlation exists between the duration of the pressure and the intensity of the bodily response. The removal of the pressure over the carotid sinus as soon as the heart rate decreased led to a slowing of the heart, followed by a return to the normal rate. No cessation of the heart beat occurred. This is shown in figure 3.

Pressure on the left carotid sinus showed a definite slowing of the heart from 80 to 50 per minute, but no cessation of the heart beat. Clinically the patient showed loss of consciousness exactly similar to that following pressure on the right carotid sinus with the heart effect as shown in figure 4.

Pressure on the vagus below the carotid sinus gave no clinical or electrocardiographic changes (figure 5). Atropine sulphate, gr. 1/50, was administered subcutaneously and pressure made over the carotid sinus 45 minutes after the administration of the drug. Figure 6, which is an electrocardiographic tracing of the

atropine effect, shows that the heart rate, which had increased from 80 to 100 after the drug administration, dropped to 60 with pressure on the carotid sinus, but did not stop at any time. The patient, however, lost consciousness and appeared to be on the verge of a convulsion. In order to study the action of epinephrine, on the following day 15 minims of a 1: 1000 solution were administered subcutaneously to the patient and electrocardiographic tracings taken 10 minutes later during pressure over the

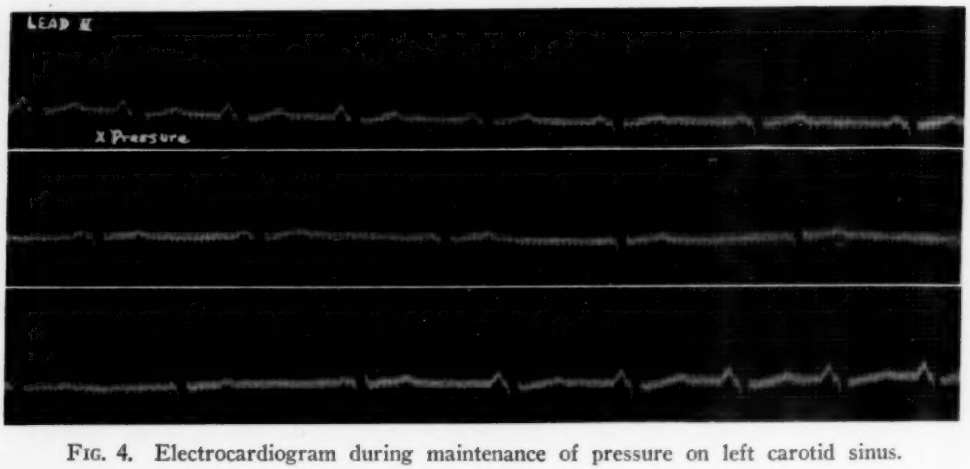

FIG. 4. Electrocardiogram during maintenance of pressure on left carotid sinus.

right carotid sinus. The heart rate slowed from 100 to 64 beats per minute but did not stop, as shown in figure 7. Clinically the patient developed dizziness but no loss of consciousness and no convulsions. Pressure over the sinuses of a series of 50 individuals in the wards suffering from a variety of other diseases failed in every case to show complete stoppage of the heart, loss of consciousness, or convulsions, although dizziness and a lowering of blood pressure were common.

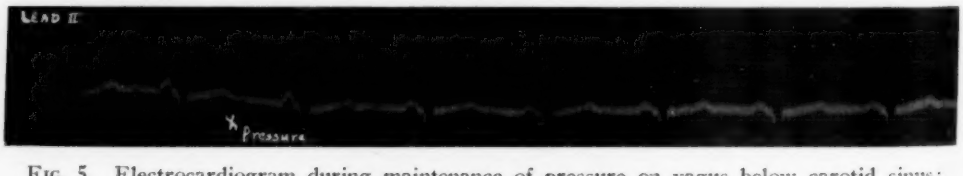

FIG. 5. Electrocardiogram during maintenance of pressure on vagus below carotid sinus; showing no electrocardiographic change.

Case 2. Another example of this interesting condition occurred in a young married Jewish female, age 28 years, who reported attacks of faintness which were preceded by yawning, dizziness, headache, nausea but no vomiting, with a gradual increase in the severity of these symptoms for 15 to 30 minutes, until the patient lost

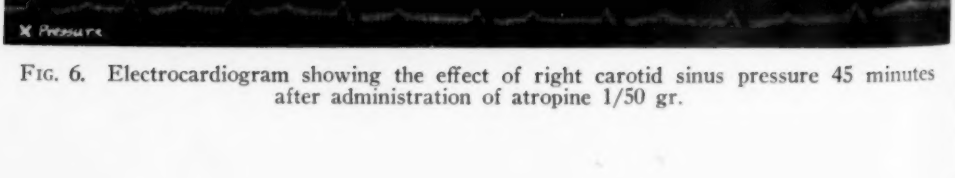

FIG. 6. Electrocardiogram showing the effect of right carotid sinus pressure 45 minutes after administration of atropine 1/50 gr.

consciousness for several seconds. Following this short period of unconsciousness there was a rapid return to a normal condition with the exception of a severe headache which usually persisted for several hours. These attacks occurred spontaneously, at irregular intervals, sometimes as often as twice a day, and at times did not return over a period of one or two months. There was no relationship of the occurrence of these attacks to the time of day, food, or physical activity. It was of interest to note that the first attack of this nature occurred during the fourth month of pregnancy.

Examination both during and between the attacks failed to disclose any of the

FIG. 7. Electrocardiogram showing the effect of right carotid sinus pressure 10 minutes after administration of epinephrine.

usual causes for this condition. Before unconsciousness occurred there was a marked pallor and frequent yawning spells with slow, deep inspirations. The pulse which was normally 76 beats, dropped gradually to six or eight beats per minute, and the blood pressure changed from 126 systolic and 80 diastolic to 60 systolic and 40 diastolic. A half hour after the patient regained consciousness the blood pressure and the pulse rate had returned to normal.

Pressure on the right carotid sinus reproduced the clinical picture observed in this patient during an attack. Pressure over the left carotid sinus gave a slowing of the pulse from 76 to 60, and a drop in blood pressure from 126 systolic and 80 diastolic to 108 systolic and 68 diastolic, but no subjective or objective changes in the clinical picture. The patient was given atropine sulphate, gr. 1/100, three times a day, and has had no attacks for seven months.

Anatomically the carotid sinus consists of a fine network of nerves surrounding the beginning of the internal carotid artery, where it comes off as a branch of the common carotid artery. The carotid sinus nerve usually lies in the posterior part of the space between the internal and external carotids. There are two main branches, one going to the vagus, and the other through the glossopharyngeal nerve to the medulla. Clinically the carotid sinus is found just below the angle of the jaw at the upper level of the thyroid cartilage when the patient is lying on the back with the head elevated and slightly retracted. Occasionally the carotid sinus is situated somewhat higher or somewhat lower.

Parry [3] (1799), Waller [4] (1862), and Czermak [5] (1866) showed that pressure over the area of the bifurcation of the carotid arteries in the neck caused slowing of the heart. They believed this to be due to direct vagus stimulation. This impression held sway for many years. In 1912 Sollman and Brown,[6] experimentally in animals, showed that the vagus apparently did not play a direct part in this reaction since an isolated small piece of the internal carotid artery, 2 cm. long, completely separated from all connections except those with the nerve plexus, gave a typical drop in blood pressure on being stretched and pulled but did not give this reaction after the connections

with the nerve plexus had been severed. Hering [7, 8] demonstrated conclusively that the slowing of the heart by digital pressure in the neck was not due to direct vagus stimulation but was the result of a reflex originating in a specialized portion of the internal carotid artery called the carotid sinus. This work was confirmed by Koch, Heymans, DeCastro, and others. Regniers, in 1930, showed that the slowing of the heart was due chiefly to a reflex action through the vagus but that there was also an inhibitory action of the carotid sinus on the tonus of the cardiac accelerator nerves. The drop in the blood pressure was due to the slowing of the heart and the inhibition of the vasomotor tonus. Schmidt [9] showed that the respiratory center in the brain is influenced not only by the chemical changes in its blood supply but also reflexly by the carotid sinus. Cutting of the sinus resulted in the abolition of the normal response of the respiratory center to anoxemia. Stimulation of the carotid sinus reflexly stimulated the respiratory center.

Pressure on the carotid sinus also gives rise to gastrointestinal manifestations such as a feeling of epigastric uneasiness, nausea and vomiting. Danielopulu found that pressure on the carotid sinus first inhibited, then increased the activity of the intestinal peristaltic movements.

In individuals with a normal carotid sinus reflex, neither complete cessation of the heart beat on pressure, nor convulsions ever occur. Koch, Hes and Mehrman, Madelstamm and Lifschitz, and Soma Weiss and Baker [10] have shown that the greatest reaction that can be obtained, even in patients who are somewhat more sensitive to pressure, as in the hypertensive or arteriosclerotic group, is a moderate slowing of the heart with a moderate drop in the blood pressure.

The cardiac arrest is due to two factors:

1. The temporary suppression of the sinus node, depriving the heart of the normal pacemaker.
2. The failure of the heart to form new foci of impulse initiation.

Persistence in pressure over the carotid sinus in a case, where complete stopping of the heart beat occurs temporarily, leads finally to the pacemaker breaking through the vagus depression with a resumption of the normal heart rate, or else to the development of a new focus usually in the ventricle which then acts as the focus for cardiac impulse initiation. The cerebral symptoms apparently are due to a vasomotor peripheral dilatation with the resultant cerebral anemia, accentuated by the slowing of the heart rate and a decrease in cardiac output with a slowing of the velocity of blood flow. Soma Weiss and Baker have shown that syncope and convulsions follow not so much as the result of the absolute degree of ischemia of the brain, as the rapidity with which this change occurs.

Whether the reflex in hypersensitive cases is the result of an abnormally sensitized state of the responsive organs with a normal carotid sinus, or a hypersensitive carotid sinus with normally responsive organs is not clearly known. Hyperactivity of the sinus is usually permanent but Weiss and Baker report two cases of recurrent hypersensitivity. The same observers

also report that local anesthesia of the sinus abolishes the ipsolateral reflex but not the controlateral reflex. In general it may be said that the hypersensitivity of the sinus is bilateral although usually the most marked effects are obtained by pressure over the right carotid sinus.

Electrocardiographic studies have shown that pressure on the carotid sinus is most frequently accompanied by an increasing A–V block, from prolonged P–R intervals to complete A–V block. This is often accompanied by ventricular extra-systoles. After the block develops, either ventricular nodal rhythm, ventricular extra-systoles, or bizarre complexes as seen in ventricular fibrillation, may occur. In our case, however, the usual findings were not present, there being at no time, from pressure over either the right or the left carotid sinus, any sign of an A–V block, either partial or complete.

Atropine paralyzes the parasympathetic or vagus nerve endings but does not affect the vasomotor reactions which take place through the sympathetic nervous system. In our case, atropine in adequate dosage removed all the vagus response except for a slight slowing which may be due to the effect of carotid stimulation in suppressing the cardiac accelerator nerves.

Epinephrine, through its property of stimulating the sympathetic nervous system, increasing the heart rate, increasing blood velocity and blood flow, stimulating the heart muscle directly, and stimulating the accelerator fibers of the heart, counteracts both the cerebral and the cardiac reactions. In our case, all reactions were abolished by epinephrine except for some slowing of the pulse, the vagus effect apparently being stronger than the epinephrine effect. Nathanson [11] has shown similar results. In addition he has also shown that ephedrine, calcium gluconate and caffeine have no effect, whereas digitalis acts to increase the cardiac effect of carotid sinus stimulation as the result of a summation effect on the A–V conduction system. Surgically, in those cases where there is a palpable mass pressing on the carotid sinus, removal of this mass will often relieve the condition. Weiss and Baker report one case where no mass could be found. The carotid nerve was cut with complete relief of the symptoms in this case. Medicinally atropine and epinephrine are the drugs of choice.

Summary

1. Two cases are presented of carotid sinus hypersensitivity.

2. Pressure on the right carotid sinus produced unconsciousness, convulsions, and cessation of the heart beat for eight seconds as shown by electrocardiogram.

3. Atropine stops the cardiac effect of carotid pressure, but not the cerebral effects.

4. Epinephrine counteracts both the vasomotor cerebral response and the cardiac response.

5. The importance of this clinical picture must be kept in mind in studying cases of so-called idiopathic epilepsy or convulsions of unknown origin.

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A CHEST ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION OF AN ENTIRE COMMUNITY *

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With pulmonary tuberculosis in the United States reaching the point where many authorities predict its early relegation to the list of minor causes of death,[1] it has become essential to protect our present low mortality levels through the study and elimination of such reservoirs of infection as are recognized to be present among our heavily infected negro population. The literature clearly acknowledges that tuberculosis in the American negro with its high mortality rate is indeed an urgent problem.[2] For many reasons the control factors which have proved so successful among our white population have found little application among the negroes. Sanatorium beds have not been provided at the same rate as for white patients. Educational facilities have been definitely less for the colored group. The economic standards of the colored race have not kept abreast of those of the white people and the consequent lower living conditions have favored undue exposures to infection and reinfection by tubercle bacilli. The presence of a notably high incidence of low grade constitutional infections among the negroes has rendered them more prone to the development of such diseases as tuberculosis. Our knowledge of inherent racial susceptibility to tuberculosis has been entirely conjectural.[3] Postmortem studies upon the lungs have been repeatedly made, however, and with the invariable finding of an undue incidence among the negroes of lesions of the exudative type, suggestive of a lack of the tendency to chronicity usually encountered in the white race.[4] In how far these findings are due to exposure of the negro to unusually massive dosages of tubercle bacilli and to what extent racial lack of resistance determines the character of the lesions it is at present impossible to state.

Opie [5] contends that there is relatively little known concerning tuberculosis as a manifest disease in the general colored population, i.e. morbidity from tuberculosis as distinguished from mortality, except by vague inference. No effort appears to have been made to determine how tuberculosis spreads among the negro group or what are the conditions which modify this spread. Yet, at Detroit, Chadwick [6] succeeded in changing the trend from an increasing to a decreasing rate by the allotment of beds for colored patients to the hitherto unobtainable rate of 1.5 beds per annual death.

* Read before Mississippi Valley Sanatorium Association, September 28, 1934, Cedar Rapids, Iowa.

Macon County, with a *total* census of 81,674, has a negro population of 1,947. Although a certain specified number of beds has never been set aside for their care, facilities for diagnosis and treatment have been available since 1923. The living standards of the negro population of Macon County are considerably better than in many other communities. During more favorable employment years there was little unemployment among them, and many were employed in industrial occupations at a fair living wage. In order to safeguard the present level of mortality from this disease (30.4 per 100,000, in 1933) and at the same time determine the actual morbidity of tuberculosis among the existing adult negro population, a roentgen-ray survey was conducted on a large scale. This method of examination was decided upon in conformity with existing opinion of phthisiologists that complete dependence may be had upon the roentgen-ray to find cases of early tuberculosis, and that all adults should be roentgen-rayed regardless of the findings of the physical examination.[7] The type and extent of tuberculous lesions present are accurately revealed by the roentgenological examination, in the opinion of Rigler,[8] and Sergent considers that " A radiological examination is an autopsy of the living."

Single chest films were made on *1,005* out of *1,232* adults, or a percentage of 81.6. All ages between 20 and 94 years were examined in the survey. The examinations were made in nearly equal proportion between the sexes. Through repeated canvassing efforts our survey yielded 89.3 per cent of examinations in that important age group 20 to 40 years. In the age group " over 60," 45.5 per cent were examined.

After completion of this roentgen-ray survey the cases showing evidence of tuberculosis were grouped as primary tuberculous infections (Ghon foci, lymph gland involvement), and manifest tuberculous disease, active and inactive. (Chart 1.) It was found that there was a surprising number of pulmonary lesions of non-tuberculous character. The incidence of abnormal cardiac silhouettes also appeared high. (Chart 2.) Out of an examined group of 1,005 negroes, 11 cases (1.1 per cent) of active manifest tuberculosis were revealed. Nine of these, or 82 per cent, were found in the age group 20 to 40. The active cases in the first age group were equally distributed between the three stages, minimal, moderate, and far advanced. (Chart 3.) Out of a total of 46 *inactive* cases, 38 showed fibro-calcareous infiltrations of the parenchyma, five pleural calcifications, and three healed miliary lesions. Evidences of primary infection as manifested by single or multiple Ghon foci and lymph node involvements, all of them showing calcium infiltration, totaled *277*, or *27.6* per cent. Lesions of clinical importance of non-tuberculous etiology were found in 38 cases, or 3.8 per cent. (Chart 4.) They included 10 cases of pneumonokoniosis, seven of passive congestion, two of unresolved pneumonia, one of chronic interstitial pneumonia, seven of bilateral basal lesions, one of bronchiectasis, four of chronic serofibrinous pleurisies, one of fibroma, three of mediastinal tumors, one of atelectasis, and one of pulmonary syphilis (tentatively diagnosed).

CHART 1

A ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933–34 (SUMMARIZED)

Ages	Sex	Number of Adults (Ages 20–94) 1933 Canvass	Examined (Roentgenograms)		Diagnosis				
			No.	%	Active	Inactive	Infection*	Non-Tbc. Pulm.	Cardiac
20–40	M	344	310	90.1	4	13	96	10	14
	F	388	343	88.4	5	5	91	7	24
40–60	M	205	159	77.6	1	12	40	11	47
	F	172	137	79.7	1	12	37	3	39
Over 60	M	61	26	42.6	0	2	8	6	13
	F	62	30	48.4	0	2	5	1	17
All ages	M	610	495	81.1	5	27	144	27	74
	F	622	510	82.0	6	19	133	11	77
Total		1232	1005	81.6	11	46	277	38	151

* As evidenced by healed Ghon foci (single or multiple) and calcified tracheo-bronchial lymph nodes.

CHART 2

A ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933–34 (CARDIAC SILHOUETTE FINDINGS)

Ages	No. Examined	Sex	Cardiac Lesions							
			Aortitis	Aneurysm	Hypertrophy	Aortic Regurgitation	Mitral Regurgitation	Mitral Stenosis	Atheromatous Plaque	Total
20–40	310	M	9	1	0	0	1	3	0	14
	343	F	13	1	4	0	3	3	0	24
40–60	159	M	37	6	2	2	0	0	0	47
	137	F	26	5	3	2	1	1	1	39
Over 60	26	M	8	3	1	1	0	0	0	13
	30	F	9	2	2	2	0	0	2	17
All ages	495	M	54	10	3	3	1	3	0	74
	510	F	48	8	9	4	4	4	3	77
Total	1005		102	18	12	7	5	7	3	151

CHART 3

A ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933–34
(TUBERCULOSIS FINDINGS—STATISTICAL)

Ages	No. Examined	Sex	Manifest Tuberculosis								Infection*			
			Active				Inactive							
			Minimal	Mod. Adv.	Advanced	All Stages	Healed Miliary	Fibro-Calc.	Pleural Calc.	Total	Ghon Focus	Multi. Ghon Foci	Calc. Lymph Nodes	Total
20–40	310	M	1	2	1	4	2	9	2	13	60	17	19	96
	343	F	2	1	2	5	0	5	0	5	56	20	15	91
40–60	159	M	0	1	0	1	1	9	2	12	32	4	4	40
	137	F	1	0	0	1	0	11	1	12	25	4	8	37
Over 60	26	M	0	0	0	0	0	2	0	2	5	2	1	8
	30	F	0	0	0	0	0	2	0	2	1	3	1	5
Total	1005		4	4	3	11	3	38	5	46	179	50	48	277
%			0.4	0.4	0.3	1.1	0.3	3.8	0.5	4.6	17.7	5.0	4.8	27.6

CHART 4

A ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933–34
(NON-TUBERCULOUS PULMONARY LESIONS—OF CLINICAL SIGNIFICANCE)

Ages	No. Examined	Sex	Non-Tuberculous Pulmonary Lesions											
			Pneumonokoniosis	Passive Congestion	Unres. Pneumonia	Chr. Interst. Pneu.	Bilat. Basal Lesions	Bronchiectasis	Pleural Effusion	Syphilis*	Fibroma	Mediastinal Tumor	Atelectasis	Total
20–40	310	M	2	1	1	1	2	0	2	0	0	0	1	10
	343	F	0	2	0	0	1	0	1	1	0	2	0	7
40–60	159	M	6	1	1	0	3	0	0	0	0	0	0	11
	137	F	0	0	0	0	1	1	0	0	1	0	0	3
Over 60	26	M	2	2	0	0	0	0	1	0	0	1	0	6
	30	F	0	1	0	0	0	0	0	0	0	0	0	1
Total	1005		10	7	2	1	7	1	4	1	1	3	1	38
%			1.0	0.7	0.2	0.1	0.7	0.1	0.4	0.1	0.1	0.3	0.1	3.8

CHART 5

A ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933–34
(MISCELLANEOUS FINDINGS—WITHOUT CLINICAL SIGNIFICANCE)

Ages	No. Examined	Sex	Non-Clinical Abnormalities						
			Irregular or Elevated Diaphragm	Eventration Diaphragm	Cervical Ribs	Bullet in Chest Wall	Dextrocardia	Empyema, Old	Total
20–40	310	M	24	2	1	1	0	1	29
	343	F	26	1	2	0	1	0	30
40–60	159	M	18	2	0	0	0	1	21
	137	F	6	5	5	0	0	0	16
Over 60	26	M	5	0	0	0	0	0	5
	30	F	1	0	0	0	0	0	1
Total	1005		80	10	8	1	1	2	102

Non-clinical abnormalities that were found, included 80 irregular, elevated, or eventrated diaphragms, eight cervical ribs, one bullet in chest wall, one dextrocardia, and two old empyemas. (Chart 5.) Among the cardiac lesions noted were 102 with important aortitis and 18 with aneurysm. One patient with aneurysm discovered on this survey, died from this cause one week following his examination.

A summary of our investigation of tuberculosis morbidity among the adult negroes discloses the following:

1. The incidence of untreated, unrecognized, non-tuberculous clinical disease is unduly high.

2. Under favorable environmental conditions the negro possesses a morbidity rate only slightly higher than that for the white.

3. In all age groups there is noted calcium deposition within the parenchymal and lung root fields which is present to a greater extent than among white people.

4. Among the discovered cases, the various stages of the disease were comparable in type to those seen in the white. In all but one instance the lesions were productive rather than exudative in type.

5. An important number of persons were found with bilateral apical, extensive fibrosis, indicative of a resistance to tuberculous infection not unlike that found in the white race.

6. The finding of a high percentage of healed primary infections, which through the years had resulted in no manifest parenchymal disease, appears significant of inherent resistance and not supportive of the older theory of racial susceptibility.

The impressions derived from this survey lead to the suggestion that tuberculosis in the negro may be controlled by the same methods that are being successfully employed for the white population inasmuch as the disease in the negro appears to be dependent upon the same factors of economy, infection, and environment. Many recent observations have served to confirm the fact that education, adequate provision of sanatorium beds and diagnostic facilities have served importantly to reduce the morbidity and mortality among this racial group.

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PLASMA CHOLESTEROL IN TUBERCULOSIS AND AMYLOID DISEASE *

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Studies of the cholesterol content of the blood in infectious diseases have shown that the acute febrile disorders,[1, 2, 3, 4] and the acute stages of syphilis,[5] leprosy [6] and tuberculosis [3, 7] are associated with hypocholesterolemia. In long standing tuberculosis, however, the blood cholesterol is not constant as in acute infections because the chronicity of the process entails complications which alter the level of the cholesterol in the blood. Variations in the blood cholesterol in phthisis are dependent on the severity of the tuberculous lesion, the body nutrition, and complications such as anemia and, as we expect to demonstrate, renal amyloidosis.

Bacmeister and Henes,[3] and Henes [4] found normal values for blood cholesterol in early tuberculosis, but an appreciable reduction was observed in advanced and fulminating cases associated with cachexia. Eichelberger and McCluskey [7] noted hypocholesterolemia in severe cases running a downhill course, and conversely, a rise in cholesterol in cases with clinical improvement. They believed these changes indicated an association between cholesterol and the degree of resistance and immunity to tuberculosis. Rosenthal and Patrzek,[8] Warnecke,[9] Szüle [10] and Macchioro [11] observed a terminal drop in the blood cholesterol. Bonnamour and Pizzéra [12] confirmed this tendency toward terminal hypocholesterolemia in tuberculosis but considered this phenomenon could scarcely yield any prognostic evidence not already shown by the clinical condition of the patient. Sayago and del Villar [13] noted a gradual increase in the blood cholesterol in patients with tuberculosis for 45 days prior to death; this finding lacks confirmation. Chauffard, Richet and Grigaut [14] observed a normal blood cholesterol in afebrile tuberculous patients, and a definite decrease in febrile cases. Monceaux [15] made an unsuccessful attempt to correlate the cholesterol variations in blood with changes in the adrenal glands in tuberculosis. Sweany, Weathers and McCluskey [16] suggested that cholesterol plays an active part in developing resistance to this disease, and von Babarczy [17] observed hypocholesterolemia in cases with increased sensitivity to tuberculin. Levinson,[18] however, could not find any evidence of increased resistance to tuberculosis in animals fed cholesterol.

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Material and Methods

Fasting blood specimens were collected in a group of 84 cases of severe tuberculosis. Determinations were made by the Sackett modification of the Bloor method [19] using the modified procedure for colorimetric estimation employed in this laboratory.[20] In some instances serial determinations were performed on the same patient. A few cases of osseous and peritoneal tuberculosis are included, although most of these patients suffered from advanced pulmonary tuberculosis with cavitation and clinical evidence of activity.

The cases studied were subdivided into five clinical groups with reference to the presence and degree of complicating amyloid disease. The Congo Red test, proteinuria, edema and renal function were the basis for the following classification:

Group I. Tuberculosis without amyloid disease (negative Congo Red test).

Group II. Tuberculosis with early amyloid disease not involving the kidneys (positive Congo Red test; no proteinuria).

Group III. Tuberculosis with early amyloidosis of the kidney (positive Congo Red test; constant proteinuria).

Group IV. Tuberculosis with amyloid nephrosis (positive Congo Red test; marked proteinuria, edema and other signs characteristic of nephrosis syndrome).

Group V. Tuberculosis and amyloid contracted kidney (positive Congo Red test; marked proteinuria; signs of impaired renal function).

Results

I. *Tuberculosis without Amyloid Disease.* There were 34 cases in this group. The predominating pulmonary lesion was ulcerative tuberculosis associated with a distinctly positive sputum and marked constitutional symptoms; two cases of bone and two of peritoneal tuberculosis were included in this series. The cases in table 1 are arranged according to the cholesterol level. Other data, such as age, extent of the tuberculous lesion and the duration, are tabulated, with a follow-up, six months after the cholesterol determination. The lowest cholesterol level occurred in one patient shortly before death in which only a trace was found (M. S.). The highest value was 286 mg. per 100 c.c. of blood. There was no apparent correlation between the plasma cholesterol and the age, extent or duration of the disease.

A striking relation between the subsequent clinical progress of these patients and the cholesterol concentrations of the plasma is evident. In all 13 cases with a cholesterol concentration below 150 mg. per 100 c.c., death followed within a brief period, generally within a month, often in a few days. In the other 21 cases with normal or slightly elevated cholesterol levels the six month mortality was 22 per cent. It is probable that a subsequent hypocholesterolemia may have occurred in the fatal cases; unfortunately serial cholesterol determinations were not made.

TABLE I

Plasma Cholesterol in Tuberculosis

Case	Age yrs.	Lesion *	Duration	Plasma Cholesterol mg. per cent	Subsequent Course †
D. R.	12	B. C. P.	1 year	286	Improved; left hospital
F. M.	25	Tb. Hip [a]	4 years	280	Unchanged
E. B.	20	B. C. P.	6 "	240	Unchanged
M. R.	16	B. C. P.	12 "	207	Died in 20 days
R. M.	28	Tb. Perit.[a]	1 "	203	Unchanged
A. H.	57	B. C. P.	1 "	196	Unchanged
H. Z.	61	B. C. P.	8 "	194	Died in 18 days
C. M.	23	B. C. P.	1 "	193	Died in 5 months
H. A.	47	B. C. P.	2 "	185	Unchanged
A. F.	28	B. C. P.	2 "	185	Improved
H. B.	50	B. C. P.	3 "	184	Improved
W. F.	40	Potts [a]	2 "	183	Died in 10 days
D. U.	38	B. C. P.	1 "	183	Died in 2 months
J. V.	25	U. C. P.	2 months	182	Improved
J. S.	54	B. C. P.	1 year	181	Died in 2 months
C. S.	73	B. C. P.	5 years	178	Left hospital in 4 mos.
J. G.	63	B. C. P.[a]	10 "	175	Unchanged
J. H.	60	B. C. P.	6 "	173	Unchanged
C. H.	62	B. C. P.	5 "	167	Unchanged
G. W.	54	B. C. P.	1 "	166	Left hospital 1 mo. later
F. C.	28	B. C. P.	2½ "	159	Improved
D. H.	23	B. C. P.	½ "	147	Died in 10 days
P. H.	61	Chr. Pro.	5 "	146	Died in 19 days
F. S.	24	B. C. P.	2 "	144	Died in 11 days
M. R.	25	B. C. P.	5 "	144	Died in 23 days
H. M.	39	B. C. P.	4 "	138	Died in 22 days
L. C.	40	B. C. P.	8 "	135	Died in 36 days
K. P.	33	B. C. P.	4 "	134	Died in 3 days
P. T.	40	B. C. P.	4½ "	122	Died in 1 day
J. B.	18	B. C. P.	4 months	118	Died in 2 days
A. H.	31	Perit. Tb.[a]	6 "	111	Died in 42 days
J. W.	35	B. C. P.	2 years	108	Died in 3 days
R. A.	26	B. C. P.	1 "	105	Died in 9 days
M. S.	24	B. C. P.	6 months	trace	Died in 2 days

For explanation of symbols see footnote table 5.

II. *Tuberculosis and Early Amyloid Disease.* This group is limited to seven cases. The diagnosis of amyloid was made by the Congo Red test and the lack of renal involvement by the absence of proteinuria.

The results shown in table 2 are essentially identical with those in table 1. Hypocholesterolemia in four cases was associated with an early fatal termination.

III. *Tuberculosis with Early Amyloidosis of the Kidney.* This group of cases had severe tuberculosis complicated by incipient renal amyloid degeneration. The amyloid involvement is recognized by a positive Congo Red test and a constant urinary protein. There were 16 cases of this type. Cholesterol values were higher in this group than in the previous ones studied. Only two cases with marked hypocholesterolemia were encountered; both of these terminated fatally within a brief period. The average

TABLE II

Plasma Cholesterol in Early Amyloid Disease

Case	Age yrs.	Lesion *	Duration years	Plasma Cholesterol mg. per cent	Subsequent Course †
E. M....	56	B. C. P.	4	217	Unchanged
J. G....	28	B. C. P.	3	193	Unchanged
C. M....	23	B. C. P.	1	193	Died in 5 months
G. L....	42	B. C. P.	2	188	Unchanged
A. P....	35	B. C. P.	2	145	Died in 1 month
A. J....	20	B. C. P.	1	133	Died in 10 days
C. S....	37	U. C. P.	3	131	Died in 16 days

For explanation of symbols see footnote table 5.

cholesterol value for the other cases was 228 mg. per 100 c.c. The six month mortality in those with normal or elevated plasma cholesterol was 22 per cent.

IV. *Tuberculosis with Amyloid Nephrosis and Edema.* Twenty patients of this type were studied. The outstanding clinical features of these cases were general anasarca and marked proteinuria. Pulmonary lesions were usually extensive and advanced. In three instances bone tuberculosis was present. Amyloidosis was recognized by the Congo Red test, and the nephrotic syndrome by the characteristic lipemia, the lowered blood proteins, the anasarca and the proteinuria.

A marked increase in plasma cholesterol, as high as 450 mg., was found; the lowest cholesterol observed at the time of edema was 200 mg. Fairly severe anemia (60 per cent hemoglobin or less) in four cases was associated with hypercholesterolemia.

When the prognosis was bad a tendency toward a falling plasma cholesterol concentration became evident; subnormal levels were noted at times. Seven cases with the nephrotic syndrome and plasma cholesterol levels of 200 mg. or less, terminated fatally within two months; those with subnormal levels died within a month. In the 16 patients with an elevated plasma cholesterol the six month mortality was 45 per cent.

V. *Amyloid Contracted Kidney.* Seven instances of impaired renal function resulting from advanced amyloid of the kidneys were studied. Impaired renal function occurred with the nephrosis syndrome in four cases. Edema was absent in the three remaining cases. No direct relationship between nitrogen retention, impaired renal function and cholesterol was evident. A falling blood cholesterol was noted in several subjects shortly before exitus. Anemia and hypercholesterolemia were co-existent in three patients.

DISCUSSION

Anemia. Subnormal blood cholesterol values have been reported in severe anemia particularly by Bloor and MacPherson [21] and Muller and

TABLE III

Plasma Cholesterol in Early Amyloid of Kidney (No Edema)

Case	Age yrs.	Lesion *	Duration years	Plasma Cholesterol mg. per cent	Subsequent Course †
M. D....	32	Potts [a] U. C. P.	6	333	Unchanged
R. F.....	14	B. C. P.	5	333	Unchanged
D. S.....	17	U. C. P.	5	330	Died in 4 months
J. M.....	24	U. C. P.	2	266	Unchanged
L. D.....	30	B. C. P.	4	224	Unchanged
P. A.....	55	B. C. P.	3	222 [b]	Died in 3 months
W. M....	43	B. C. P.	4	200	Unchanged
M. K....	24	B. C. P.	10½	200	Unchanged
S. T.....	45	B. C. P.	4	200 [b]	Died in 2 months
A. H.....	57	U. C. P.	4	196	Unchanged
C. I.....	15	Bone Tbc. [a]	6	176	Unchanged
W. B....	20	Potts [a]	12	175 [b]	Unchanged
J. G.....	63	B. C. P.	10	175	Unchanged
J. D.....	38	B. C. P.	3	172	Unchanged
W. G....	69	B. C. P.	3	147	Died in 2 months
M. P....	48	U. C. P.	7	127 [b]	Died in 1 month

For explanation of symbols see footnote table 5.

TABLE IV

Plasma Cholesterol in Renal Amyloid (with Edema)

Case	Age yrs.	Lesion *	Duration years	Plasma Cholesterol mg. per cent	Subsequent Course †
N. D....	22	B. C. P.	4	407	Living
M. K....	25	B. C. P.	3	340	Died in 1 month
W. B....	33	B. C. P.	5	331 [b]	Left hospital (in extremis) after 3 months
E. S.....	46	B. C. P.	4	300	Living
R. R.....	27	B. C. P.	6	290	Living
J. G.....	21	B. C. P.	3	290	Living
V. I.....	17	B. C. P.	2	284	Living
S. B.....	21	Potts [a]	3	280	Living
E. H.....	7	Potts [a]	1½	280	Died in 1 month
E. C.....	39	U. C. P.	2	265	Living
A. D.....	39	B. C. P.	2½	250 [b]	Died in 4 months
B. K.....	47	B. C. P.	4	240 [b]	Living
M. V.....	20	B. C. P.	1	212 [b]	Living
J. B.....	18	B. C. P.	8	200	Died in 1 month
K. G.....	22	B. C. P.	2	200	Died in 1 month
N. P.....	45	B. C. P.	2	200	Died in 3 months
M. W....	29	B. C. P.	2	177	Died in 2 months
J. D.....	54	B. C. P.	1	177	Died in 3 months
D. D.....	15	Potts [a]	5	160	Died in 1 month
W. C....	53	B. C. P.	3	160	Died in 1 month

For explanation of symbols see footnote table 5.

TABLE V.

Plasma Cholesterol in Amyloid with Impaired Kidney Function (Amyloid Contracted Kidney)

Case	Age yrs.	Lesion *	Duration years	Kidney Function	Plasma Cholesterol mg. per cent	Subsequent Course †
‡ F. H...	49	B. C. P.	3	Terminal increase in N. P. N. to 76 mg.	450	Died in 4 months
‡ J. D....	27	B. C. P.	4	Urea—N 36 mg.; low urea clearance	347 [b]	Died in 2 months
‡ J. B....	45	B. C. P.	4	Sudden elevation in N. P. N. to 90 mg.; impaired 2 hour test	258 [b]	Died in 4 months
‡ S. W...	26	Tbc. osteomyelitis	12	N. P. N. 110 mg.	234 [b]	Alive
W. O....	28	B. C. P.	4	N. P. N. 76 mg.; impaired 2 hour test	177	Alive
M. M....	47	B. C. P.	4	Terminal increase in N. P. N. to 70 mg.	145	Died in 2 months
S. K.....	32	B. C. P.	5	Increase in N. P. N. to 63 mg.; impaired 2 hour test; uremia	(194) § (127) § 97	Died in 3 days

[a] *Sputum* negative. Positive in all other cases.
[b] *Severe anemia* (Hgb. less than 60 per cent).
* *Lesion:* B. C. P.—bilateral caseous pneumonic tuberculosis; U. C. P.—unilateral caseous pneumonic tuberculosis; Chr. Pro.—chronic productive tuberculosis; Perit. Tb.—peritoneal tuberculosis.
† *Subsequent course:* Clinical condition 6 months after cholesterol determination.
‡ *Edema* present (nephrotic syndrome).
§ *Previous* determinations.

Heath.[22] Since anemia often develops in a chronic debilitating disease, such as tuberculosis, this complication should be considered whenever hypocholesterolemia exists. The anemia did not appreciably affect the blood cholesterol in this series; on the contrary, in patients with proteinuria and edema an elevated plasma cholesterol was always found irrespective of the severity of the anemia. Cholesterol variations due to anemia in tuberculous affections complicated by amyloid, are of minor significance compared to the primary influence of inanition, cachexia and the abnormal lipoid-protein metabolism of edematous renal disease.

Lipemia in Edematous Amyloid Nephritis. A rise in the blood fats and cholesterol is characteristic of the edematous forms of Bright's disease known as "lipoid nephrosis" and the "nephrotic" type of glomerular nephritis. Such a nephritic lipemia is usually ascribed to an unusual mobilization of fat in the blood rather than to a defective absorption of oxidation of fat.[23] Fishberg [24] cites the experimental work of Boggs and Morris who induced lipemia and hypercholesterolemia in animals by repeated bleedings; he believes that this lipemia follows the diminution of the blood proteins

brought about by the loss of blood. Fishberg [25] noted a direct relation between blood lipoids and the plasma proteins and considered the lipemia a compensatory process for the maintenance of normal osmotic pressure. The results of Leiter [26] with plasmaphoresis and Shelburne and Egloff [27] with starvation fail to reveal any permanent or striking relation between blood proteins and cholesterol.

The increased blood cholesterol in amyloid disease of the kidneys with edema is presumably identical with that of the edematous forms of nephritis. It is noteworthy that hypercholesterolemia preceded the appearance of edema in cases of amyloid nephrosis with marked proteinuria.

A high blood cholesterol is unusual in tuberculosis without amyloid. In the absence of proteinuria, a normal or slightly elevated cholesterol level persistently maintained is a favorable prognostic sign. Conversely, a low or falling cholesterol level in tuberculosis is a reliable indication of an early fatal termination. Death occurred within several months, even within several weeks, in 14 cases having a plasma cholesterol level below 150 mg. A prognosis judged by clinical signs was forecast less accurately than when the blood cholesterol was used as a guide.

It is evident that in tuberculosis complicated by amyloid the proteinuria is the important factor depleting plasma proteins and resulting in lipemia. Thus early amyloid without renal involvement (absent proteinuria) has no appreciable effect upon the blood cholesterol in tuberculosis. The blood cholesterol rises before edema develops in cases of amyloid of the kidneys with marked proteinuria. Hypercholesterolemia is most marked in cases of renal amyloid with edema (nephrosis syndrome). This is associated with the markedly diminished protein content of the blood which occurs in this condition as a result of the prolonged protein loss through the kidneys; cholesterol levels as high as 450 mg. were observed.

The elevated plasma cholesterol does not increase the resistance to the tuberculous process. The fact that 45 per cent of the nephrotic group with elevated cholesterols terminated fatally within six months indicates this. These clinical observations confirm the experimental results of Levinson previously cited. In these cases there is a tendency towards a pre-mortal drop in plasma cholesterol. Seven patients with blood cholesterol levels of 200 mg. or less died within two months. When the nephrosis syndrome is present a normal cholesterol level is an indication of a diminishing cholesterol curve and has the same significance as actual hypocholesterolemia.

Epstein and Rothschild,[28] Schmidt,[29] Henes,[30] and Ashe and Bruger [31] observed a drop of the blood cholesterol in terminal uremic states. The cachexia incident to marked impairment of kidney function or to advanced tuberculous disease has the same depressing effect upon the level of the blood cholesterol.

Conclusions

1. A maintained subnormal level of plasma cholesterol in tuberculosis is a serious prognostic sign signifying an early fatal termination.

2. Renal amyloid disease with marked proteinuria is accompanied by a progressive increase in plasma cholesterol which precedes the development of clinical edema. This hypercholesterolemia occurs even in the presence of severe anemia.

3. The elevated plasma cholesterol in cases of renal amyloidosis does not appear to exert any protective influence against the underlying tuberculous infection.

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ARTERIOSCLEROSIS IN DIABETES

I. RELATIONSHIP BETWEEN PLASMA CHOLESTEROL AND ARTERIOSCLEROSIS. II. EFFECTS OF THE HIGH CARBOHYDRATE–LOW CALORIE DIET *

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Definition of age is difficult. Of the many available, the anatomical definition is, perhaps, the best. Gross [1] has clearly shown that, in embryonic life, the right side of the heart has a greater vascular tree than the left, and this relationship persists for some time after birth. As it assumes greater activity, however, the left ventricle becomes more and more richly supplied with blood, and with each succeeding decade, there is such an alteration of the vascular architecture that, at the seventh decade, the left-sided vasculature so overshadows that of the right as to point toward a relative right-sided anemia. As a protective mechanism against the possible obliteration of a large vessel, the patency of the arterie telae adiposae gradually increases. These vessels may eventually be capable of bearing the brunt of obliteration of even a main coronary artery. More recent studies also indicate the development of a vascular communication in the muscle of the heart. The findings thus suggest that, as age progresses, the chief danger is a relative right-sided anemia. The effect of the total change has been very succinctly summarized in the expression—A man is as old as his right coronary artery. This is a postmortem finding. Clinically, according to the electrocardiograph and also according to other postmortem data, it would now appear that the "artery of sudden death"—that which is most often affected by sclerotic changes, thrombosis, and embolism—is the anterior descending branch of the left coronary artery. Both findings, however, support the adage that "a man is as old as his arteries."

If alteration in vascular architecture is even approximately a characteristic of age, it would appear that the condition of the diabetic is now a happy one; the diabetic now lives long enough to enable the architecture to change. The high incidence of cardiovascular disease in diabetes mellitus has been commented upon repeatedly. Cardiovascular disease has replaced coma as one of the chief causes of death. There is, however, this disturbing difference: coma was the result of uncontrolled diabetes; whereas, cardiovascular disease, apparently, develops in spite of control; it develops whether the urine is, or is not, free of sugar and whether the blood sugar is, or is not, normal. It is equally disturbing that it is not confined to elderly people and that only five years is the usual time necessary for its develop-

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ment; with diabetes of five years' duration, arteriosclerosis has developed regardless of the age; the frequent finding of calcification of arteries and other signs of arteriosclerosis in children is evidence of this fact.

In a recent study of 500 carefully examined patients in our clinic [2] the incidence of cardiovascular disease was found to be 62.6 per cent. That the actual incidence is probably still greater is suggested from our experiences with a number of methods of examination when used singly and in combination with each other for the detection of vascular disease; and from a comparison of the *combined* method which we finally adopted, with careful postmortem studies. The combined method of examination shows the high incidence of cardiovascular disease among young diabetics. Thus, when grouped according to age (see table 1) 54.7 per cent of the

TABLE I

Incidences of Cardiovascular Disease among 500 Diabetics According to Age

Age Period	Number	Cardiovascular Disease	
		Number	Per Cent
–10	4		
11–20	14	4	28.6
21–30	34	5	14.7
31–40	67	33	49.2
41–50	124	91	73.3*
51–60	158	106	67.1
61–70	80	59	73.7
71–80	18	14	77.8
81+	1	1	—
	500	313	62.6

* *Note:* Among 243 individuals of 50 years of age and under, cardiovascular disease was found in 133—an incidence of 54.7 per cent.

patients of age 50 years and under had vascular disease; and for the same age-group, of 108 autopsies, Shields Warren [3] found arteriosclerosis in 71 cases—an incidence of 65.7 per cent. Particular attention is drawn to the younger diabetics since, after 50 years of age, a high incidence of vascular disease is expected in all people, diabetic or nondiabetic.

The direct cause of the high incidence of vascular disease among diabetics is unknown. The contributing factors, however, appear to be many. Race and heredity operate in the diabetic as well as in the nondiabetic and, as stated previously, the duration of the diabetes is an important influencing factor. In the above mentioned investigation [2] we found that, with the disease of five years' duration or more, and regardless of the age of the individual and severity of the diabetes, over 80 per cent of our diabetics had cardiovascular disease. Thus (see table 2) of 144 diabetics who had the disease for five years or more, 121 were found to have arteriosclerosis, regardless of age—an incidence of 84 per cent; and of 81 individuals of age 50 years and under, but also with diabetes of five years or more, 69 had

TABLE II

Relationship between Cardiovascular Disease, Age and Duration of Diabetes among 500 Diabetics

Period	Duration of Diabetes					
	5 Years and Over			Under 5 Years		
	Total Number	Cardiovascular Disease *		Total Number	Cardiovascular Disease	
		Number	Per Cent		Number	Per Cent
−10				4		
11–20	2	2	100.0	12	2	16.7
21–30	4	2	50.0	30	3	10.0
31–40	21	18	85.7	46	15	32.6
41–50	54	47	87.0	70	44	62.8
51–60	50	43	86.0	108	63	58.3
61–70	12	8	66.7	68	51	75.0
71–80	1	1	100.0	17	14	82.3
81+				1	1	100.0

* *Note:* Of 81 diabetics of age 50 years and under, 69 had arteriosclerosis—an incidence of 85.1 per cent.
Of 144 diabetics of all ages combined, 121 had arteriosclerosis—an incidence of 84.0 per cent.

signs of vascular disease—an incidence of 85.1 per cent. The discovery of this high incidence of cardiovascular disease with the diabetes of five years' duration or more was due, as we have shown, to our combined method of examination; and that it very closely approximates the truth is suggested from postmortem findings; in his monograph on the pathology of diabetes mellitus, Shields Warren [3] who has made a special study of diabetes, states "I have yet to see at autopsy a diabetic, or to read a protocol of a diabetic, whose disease has lasted 5 years or more, free from arteriosclerosis, regardless of age." Fortunately, however, as I believe the data to be presented here suggest, cardiovascular disease, in the young diabetic at least, is not inevitable. The diabetic, as well as the nondiabetic, must die eventually. *Premature* development of arteriosclerosis, however, appears to be a preventable condition; the data clearly indicate that the condition can, at least, be delayed.

That the high incidence of cardiovascular disease noted in the past may have been due, to some extent, to the methods of treating diabetes, has been suspected for some time. I am referring particularly to treatment with diets of low carbohydrate and high fat content. Shepardson [4] in a study of arteriosclerosis in young diabetics, observed "a striking parallelism between the reduction in average values of blood cholesterol and the reduction in the incidence of arteriosclerosis." Joslin has had the impression for some time that excess fat in the diet may be a factor in the premature development of arteriosclerosis [5] and that, in his clinic, arteriosclerosis is decreasing

with the more liberal use of carbohydrates. In a letter to me, Dr. Joslin writes " since the use of 100 grams or more of carbohydrate with my diabetic patients, I believe the development of arteriosclerosis has been postponed. It is difficult to prove this statistically because now patients live so much longer than formerly, that even without diabetes many would be showing arteriosclerosis. With children there is definitely less arteriosclerosis than formerly." These impressions fit in with the fairly well established fact that continual feeding of large quantities of fatty substances and of cholesterol leads (at least in herbivora) to deposition of fatty materials in the intima [6] and, it should here be observed, that lipoid infiltration of the intima is the outstanding vascular lesion in the young diabetic.

That excess cholesterol in the blood, if not the direct agent, may at least be an important contributing factor in the production of arteriosclerosis in the diabetic has been suggested repeatedly. In their " Quantitative Clinical Chemistry," Peters and Van Slyke [7] state that " there is little or no evidence to support such a theory. Hypercholesterolemia is not observed with any regularity in arteriosclerosis." As I shall presently show, however, this observation is not in accord with a number of known facts.

There is, firstly, the evidence of the pathologist. I have referred to lipoid infiltration of the intima. This is a characteristic of the atheromatous type of vascular disease—the type which is very common in diabetics; and vascular disease in diabetes is largely confined to the intima, regardless of its site—heart, extremities, etc. There is also the observation of Klotz and Manning [8] concerning the association of fatty deposition in the intima with definite age periods; it is very frequent between age 20 and 30 years and unusual before age 10 and after age 50 years. This, it should be noted, fits in with the previously mentioned high incidence of vascular disease in the diabetics of age 50 years and under. Aschoff [9] attributed the atheromatosis of diabetes mellitus to deposition of lipoid materials in the arteries. The lipoids, according to Aschoff, may not be the direct cause of the atheromatous changes, but they can influence the course of the disease by determining the degree of fatty infiltration of the hyalinized ground substance. Shields Warren [3] put it this way: " The lipoids are not the first wave of the assault. They are the reinforcements that consolidate the gains made by the attacking force. The normal intima is not disturbed by fat . . . but given an abnormal intima, atheromata will develop in proportion to the amount of fatty substances present." Labbé and Heitz [10] believe that obliteration of the arteries in diabetes mellitus is due to localization of cholesterol in the intima.

There is the evidence of chemical pathology. Windaus [11] compared cholesterol contents of normal with diseased aortae and found the diseased vessels contained at least six to seven times as much free cholesterol as the normal and between 20 to 26 times as much cholesterol esters. Selig [12] found between 3 and 4 per cent ether-soluble matter in normal aortae; whereas, atheromatous aortae yielded up to about 15 per cent of

fatty substances. In three atheromatous vessels, Ameseder [13] found that, of the "total fat," a very large portion—28.56 per cent—was unsaponifiable matter, chiefly cholesterol. The high cholesterol content in atheromatous aortae has been confirmed by other workers.[14, 15] The case reported recently by Cullinan and Graham [16] is probably the most striking example of this condition. A young male, who had diabetes eight and one-half years, died of *coronary thrombosis* at the *age of 27* years. This, as the authors pointed out, appears to be the first case with such widespread arterial degeneration and death from coronary thrombosis at such an early age. The cholesterol content of the dried aorta was 5.8 per cent; whereas, the aorta of a young nondiabetic female of about the same age (30 years) contained only 0.64 per cent. These authors also record the finding of 10.4 per cent cholesterol in the dried aorta of a male, aged 66 years, with advanced atheroma.

In addition to the observations on pathology and pathological chemistry, there is the chemistry of the blood. Hypercholesterolemia is a common metabolic finding in diabetes mellitus. Earlier analyses,[17, 18] however, failed to reveal any characteristic abnormalities in the blood lipoids in patients with arteriosclerosis. In 1925, Pribram and Klein [19] found an increase of blood cholesterol in this condition; and, in the same year, Labbé and Heitz [10] reported the finding of hypercholesterolemia in a case of endarteritis obliterans in a diabetic. Mjassnikow [20] found it regularly in advanced arteriosclerosis of the aorta and coronary arteries. In 1927, I reported findings in 16 cases of gangrene; the average cholesterol content of the blood plasma was 0.344 per cent and only one of these diabetics had a cholesterol of less than 0.200 per cent.[21] In 1929, I pointed out the high incidence of vascular disease among our patients with excess quantities of cholesterol in the blood.[22] In their earlier studies, Joslin [23] and Hunt [24] failed to find a relationship between circulating blood cholesterol and arteriosclerosis among diabetics. However, this is not in conformity with later reports from the same clinic; according to White and Hunt [25] arteriosclerosis in the vessels of the legs was discovered by roentgen-ray in nine of 48 children in whom examinations were made; and hypercholesterolemia was found in 46 per cent of the cases studied. The average cholesterol of all analyses preceding, coincident with, and following the discovery of the arteriosclerosis in the 9 children was 0.263 per cent. In his recent address on "Fat and the Diabetic" Joslin [26] summarizes his experiences with children thus: Cataract and arteriosclerosis were many times more common among children with hypercholesterolemia than with normal cholesterol; nine of eleven children had high cholesterol values prior to the discovery of the arteriosclerosis; and in the subsequent courses of 67 children with high cholesterols, arteriosclerosis developed in 15 per cent; cataract in 8 per cent and nephritis in 6 per cent. In the same address, Joslin also quotes Bloor as having found "higher values for cholesterol in the arteriosclerotic diabetic than in those without sclerosis." The finding of hypercholesterolemia with cataract is of interest, in view of the previous observation by O'Brien and Myers [27] that blood cholesterol was

found elevated in 54 per cent of cases of senile cataract. It would thus appear that my earlier findings have been amply confirmed.

The finding of normal quantities of cholesterol in cases of advanced arteriosclerosis, particularly of the atheromatous type, does not appear to fit in with a causal relationship between this blood lipoid and vascular disease. This, however, in my opinion, does not *disprove* such relationship. The finding of a normal amount of cholesterol in the blood does not necessarily imply that the cholesterol is harmless. Whether cholesterol does, or does not, deposit in the intima, may depend largely upon its physical state. Bloor's observation [28] is of interest here. *"Deposition of cholesterol and its esters does not necessarily require a high cholesterol, but depends upon the ability of the blood to keep in solution a substance which is probably in a state of supersaturation."*

Interpretation of the above data is, however, not simple. As Shields Warren [3] has pointed out, mere association of high cholesterol with arteriosclerosis is not enough. Otherwise, every time we eat a fat-rich meal, particularly eggs,* a bit of arteriosclerosis would be added. Causal relationship is, however, suggested from a variety of other data, particularly the results of experiment.

Since 1908, when Ignatowski produced arteriosclerosis by feeding rabbits with protein, much has been done with respect to experimental production of arteriosclerosis; and it was in 1912 when Anitschkow, in Leningrad, produced typical atherosclerosis in rabbits by the administration of pure cholesterol in olive oil. This was an important advance, since cholesterol atherosclerosis resembles very closely the atherosclerosis of man. For an excellent review of this subject, the reader is referred to the recent publication on arteriosclerosis by the Josiah Macy Jr. Foundation.[29] In addition to these data, there is the recent work of Leary † [30] namely, the production of coronary atherosclerosis in rabbits comparable with the lesions found in man. What may prove to be of therapeutic value and also supports the view that the relationship between arteriosclerosis and blood cholesterol is causal and not accidental are the findings of Turner [31] and of Turner and Khayat.[32] These workers found that administration of thyroid gland simultaneously with cholesterol prevented atheromatous changes produced by the latter in 17 of 19 animals; potassium iodide also exerted a strong protective action; thyroidectomy in itself did not cause a rise of blood cholesterol or lead to atherosclerosis. Potassium iodide failed to exert a protective action when the thyroid gland was removed. In these experiments a relationship was found between the level of circulating cholesterol and the development of atherosclerosis.

* A large egg contains about 0.4 gram of cholesterol.

† Leary points out that man is apparently the only animal that dies in life from coronary disease and almost universally acquires atherosclerosis in later life. It is also of interest here to note that, compared with nondiabetics of similar age, the incidence of coronary disease in diabetes is high. In 270 postmortem examinations, Shields Warren [3] found coronary sclerosis in 124 cases—an incidence of about 46 per cent.

The problem of cholesterol and arteriosclerosis is obviously a very difficult one and is further complicated by the fact that so little is known of cholesterol itself. This applies both to its chemistry and physiology. Strictly, cholesterol is not even a fat. Though it is classified as a lipoid, it is included among the latter group of substances largely because of its physical properties (solubility, etc.). As found in the body, it is probably not even a chemical individual. There is much to support the view that so-called cholesterol consists of two or more sterols differing in melting point, power to absorb ultra-violet light, precipitability and other properties. As stated, little is also known of its functions in the body, but that it is an essential constituent of protoplasm is suggested from its widespread distribution in nature.[33] As Bills [34] put it in his recent review of the physiology of the sterols, cholesterol occurs in the most diverse phyla of the animal kingdom, and if one can reason from the general to the specific, it would appear to be absent in no metazoa except the sponges and certain mollusks, and in these to be represented by one or another of the allied spongosterols or ostreasterols.

How excess cholesterol might lead to arteriosclerosis is not clear. Some time ago, from data I obtained on the colloidal osmotic pressure of the blood in diabetes mellitus,[35] I suggested increase of colloidal osmotic pressure in the capillaries as a possible cause. Though there was little direct evidence, the sum of all data (clinical and laboratory) then available tended to support the view that, in diabetics with hypercholesterolemia, an osmotic pressure greater than normal is constantly exerted in the capillaries. To overcome the latter, for purposes of renal excretion, a greater hydrostatic pressure is required; this increased pressure, though relatively small, when continued over a long period of time might have the same effect as more marked intracapillary pressure exerted over a short period of time. In animals, the latter when produced either by injection of epinephrine or by sympathetic stimulation, is alleged to cause arteriosclerosis. It is difficult, however, to reconcile this view with cases of arteriosclerosis without increase of blood pressure; and it is this type of arteriosclerosis which is common among diabetics, particularly in the younger age groups. More recently, I suggested hypervitaminosis as another possible cause.[36] This view was based upon a variety of data, namely, (*a*) the known action of irradiated ergosterol, (*b*) the intimate association of ergosterol with cholesterol, (*c*) the cholesterol content of the normal skin, (*d*) the high sterol content of the diabetic skin and, lastly, (*e*) the action of solar rays and artificial radiation on the skin. Combining these observations, it appears reasonable that the tissues of the diabetic with hypercholesterolemia are being bombarded continuously with excess quantities of irradiated ergosterol and thus are exposed to excess calcification. The high incidence of arteriosclerosis in diabetes with xanthosis [37, 38] is very suggestive. Hess, Weinstock and Helman [39] have suggested that the relatively high concentration of sterols in the skin and subcutaneous tissues is a provision for the more

direct exposure of the contained ergosterol to the activating light rays of the sun. Opposed, however, to hypervitaminosis is a characteristic of vitamin D, namely, the wide range between its ordinary therapeutic dose and that which is capable of producing vascular changes. Also, there is the fact that calcification of the arteries due to excess exposure to vitamin D centers largely about the media; whereas, the dominant vascular disturbance in diabetes is, as stated, in the intima. A number of factors may, however, operate together. Thus, combining their experience with cholesterol in hyperthyroidism and hypothyroidism with the observations by Aub, Bauer, Heath and Ropes [40] on calcium excretion in the same conditions, Mason, Hunt and Hurxthal [41] have suggested that arteriosclerosis in the diabetic may be due to a combination of excess cholesterol and diminished excretion of calcium.

Results of a Statistical Study of the Relationship Between Blood Cholesterol and Cardiovascular Disease

Before attempting to relate blood cholesterol to arteriosclerosis, it is necessary to consider conditions other than arteriosclerosis which may influence blood cholesterol. As will presently be shown, though the finding of hypercholesterolemia may suggest a causal relationship between arteriosclerosis and blood cholesterol, normal quantities of cholesterol do not necessarily exclude such relationship. A possibility which must be considered is that, in such a case, the individual may have had excess quantities of cholesterol in the blood for some time and thus have developed arteriosclerosis; but, at the time of examination, there may have been some condition which lowered the concentration of this blood lipoid.

To the end of 1933, we have made 5151 observations on plasma cholesterol among our diabetics. In practically all of the cases, the blood samples were collected under the same conditions with respect to preparation of patients; with extremely few exceptions, all bloods were collected in the fasting state. The purpose of this routine is to eliminate one important variable in the interpretation of cholesterol data, namely, the influence of food. It should here be observed that the cholesterol content of the blood may be appreciably affected by quantity and kind of food. As a rule, it is increased, the increase depending to some extent upon the type of food taken [42] though it is not necessarily due to the cholesterol content of the food. At times, there may be no increase in the total blood cholesterol content, but an *alteration of the ratio of free cholesterol to cholesterol* esters.[43] This, as will presently be shown, is an important consideration, in view of the method used for the estimation of blood cholesterol.

Though all blood samples were collected in the fasting state, the conditions were not strictly basal; bed patients only were at rest. Exercise is known to increase blood fat.[44] However, the amount of exercise must be quite appreciable and, in general, though exercise may increase the fat content of the blood, there is generally little or no change in cholesterol.[45]

The method we use routinely, and by means of which the data in this investigation were obtained, is based upon a reaction which is affected by free cholesterol as well as its esters, namely, the Liebermann-Burchard reaction. The test thus reflects the *total* concentration of cholesterol in the blood. It does not, however, entirely eliminate all possibility of error. The Liebermann-Burchard reaction is a color reaction and the amount of color developed depends not only upon the total amount of cholesterol, but on the proportions of free cholesterol and cholesterol esters; it appears to be greater with the esters than with a corresponding amount of free cholesterol.[46] Blood samples must, therefore, be collected under conditions in which the ratio of free cholesterol to its esters is fairly constant. By avoiding the effects of food and severe exercise, this source of error is largely eliminated. However, as will presently be shown, aside from the above mentioned variables, there are other sources of difficulty in the interpretation of plasma cholesterol. A summary of all of our data is shown in table 3.

TABLE III

Average Annual Plasma Cholesterol *

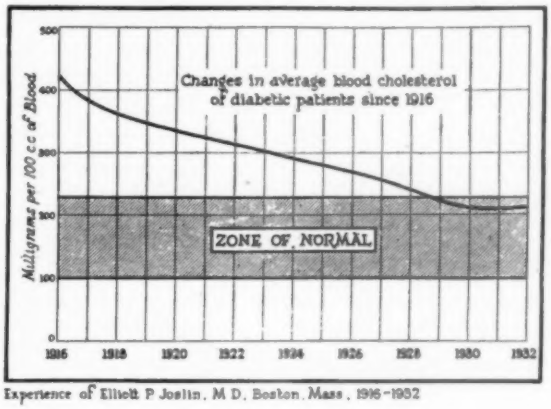
	Joslin Clinic	Montreal Gen. Hosp. Data	
Year	Average † Cholesterol (Per Cent)	Number	Average Cholesterol (Per Cent)
1926	0.270	297	0.270
1927	0.257	570	0.247
1928	0.240	498	0.275
1929	0.220	441	0.258
1930	0.215	1092	0.214
1931	0.210	936	0.228
1932	0.212	722	0.228
1933		595	0.207

* Includes admission, discharge and progress data.
† Data from Joslin Clinic. Chart 10. Metropolitan Life Ins. Co.; 1933 Report: The Control of Diabetes (3000 analyses in 1100 cases).

It will be observed that the cholesterol values are grouped according to the year in which they were obtained. The purpose of this grouping is to show the trend of blood cholesterol, namely, the decrease within recent years; the averages found between 1930 and 1933 were lower than those noted between the years 1926 and 1929. These findings agree, in general, with Joslin's experiences. The latter are reproduced in the same table and were taken from a report (chart 1) published by the Metropolitan Life Insurance Company to portray the success obtained in the control of diabetes.[47] . . . " The fall of the blood cholesterol to normal," this report states, " is further evidence of the recent improvement in diabetic treatment."

The purpose of recording the above summaries of Joslin's and our own data is to demonstrate a number of difficulties in the interpretation of blood cholesterol observations which had to be considered in this study of arterio-

sclerosis. As I shall presently show, neither Joslin's data nor our own, as shown in this table and chart 1, necessarily indicate improvement in methods of treatment. Both Joslin's data * and our own, for example, include *all* cholesterol determinations, that is, those made *before* and after treatment.



Experience of Elliott P Joslin, M D, Boston, Mass, 1916-1932

CHART 1

One source of error is, therefore, immediately obvious; a normal cholesterol found *before* treatment must obviously not be attributed to improvement of method of treatment.

In table 4 are recorded all of our data which were obtained when the

TABLE IV
Annual Average Plasma Cholesterol *

Year	No.	Average Cholesterol (Per Cent)
1926	62	0.348
1927	43	0.354
1928	59	0.325
1929	101	0.301
1930	207	0.282
1931	284	0.288
1932	216	0.263
1933	187	0.242

* Includes data obtained on admission only.

patients were first admitted to our clinic, that is, before any form of treatment was given in the majority of cases and in every case before having been subjected to our methods of treatment. Here, it will be noted, that, for the corresponding years, the average values are higher than in table 3, but, again, the values between 1926 and 1929 are *higher* than between 1930 and 1933. Since the great majority of these patients received no intensive treatment prior to their admission to the clinic, it is obvious that the de-

* Personal communication.

crease of cholesterol must have been due to some condition, or conditions, other than treatment. One of these conditions is early diagnosis. This is shown in table 5, in which are recorded plasma cholesterol determinations

TABLE V

Influence of Early Diagnosis upon Plasma Cholesterol

Type of Case	No.	M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
Ward diabetics (1933)	187	242	86	4.23			
					30	5.73	5.2
Life assurance cases	163	212	73	3.84			
					46	5.40	8.5
Potential diabetics	128	166	65	3.80			

M = Mean (average cholesterol—mg. per 100 c.c. plasma).
σ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

in 478 individuals who *at no time received any treatment* before their admission to the Clinic. The cases are divided into three groups as follows:

Group 1 consists of cases of *fully established diabetes;* that is, the diabetes was sufficiently advanced to have warranted admission of the patients to the hospital wards for intensive treatment.

Group 2 consists of cases of diabetes in its very *early stages,* that is, individuals with no signs or symptoms of the disease, in whom the glycosurias were discovered accidentally when these people applied for life assurance policies.

Group 3 consists of individuals who may be regarded as *potential* diabetics only. *Glycosuria was never found in any of these individuals.* The disturbances of carbohydrate tolerance, in this group, were suspected because of a variety of clinical conditions, eczema, neuritis, etc. On careful investigation, many of these individuals were found to have had very mild hyperglycemia only in the fasting state. In the remainder of the group, the blood sugars were normal in the fasting state; but the disturbances of carbohydrate tolerance were discovered by obtaining blood sugar time curves following ingestion of glucose.

The above grouping clearly shows the importance of early diagnosis in the interpretation of cholesterol data; as the diabetes became more fully established, and, as no treatment was given, the cholesterol content of the plasma increased. It should be observed that the differences noted between the average cholesterol values of the different groups are statistically significant. This is shown in each case, by the ratio of difference to its probable error.*

* In this, and the following studies, a ratio of difference to its probable error less than 3.0 was not regarded as significant. With a ratio of 3.0, it can be shown that the odds against the occurrence of a difference of such magnitude being due to chance alone are about 20 to 1.

It will be noted that the average cholesterol in the group of potential diabetics (0.166 per cent) was lower than that of normal individuals (0.180 per cent). The probable explanation is that, in a number of these cases, there were conditions which tend to lower blood cholesterol. None of these individuals, it should be observed, was perfectly normal. This would probably also apply to the group of ward diabetics, though not to the life assurance applicants, the majority of whom may be assumed to have been healthy. These data, may, therefore, not be strictly comparable, but they appear to be sufficiently so to show the force of early diagnosis.

Table 6 shows another variable which must be considered in the inter-

TABLE VI

Immediate Effects of Treatment upon High Concentrations of Plasma Cholesterol

Subject	Plasma Cholesterol (Per Cent)		
	Admission	Discharge	Decrease
5728/28	1.380	0.504	0.876
6535/28	1.190	0.520	0.670
2126/29	0.926	0.438	0.488
3345/29	1.510	0.640	0.870

pretation of plasma cholesterol, namely, the *immediate* effects of treatment upon *very high* concentrations of plasma cholesterol. The marked and rapid decreases of cholesterol clearly demonstrate the error of drawing conclusions from averages based upon a small number of observations. High cholesterol values, as shown in this table, may be met with in very acute forms of diabetes and in cases of acidosis. All of the cases shown in this table were cases of diabetes with ketosis and acidosis.

A variety of other conditions may influence plasma cholesterol; such conditions as alcoholism, nephrosis, gout, pregnancy, biliary obstruction and myxedema are associated with an increase; whereas, febrile disorders, hepatitis, severe anemias, cachexias in general, syphilis, tuberculosis and hyperthyroidism tend to lead to a decrease. In the female, consideration must also be given to the general increase before, and fall during, menstruation.[48] Tables 7 and 8 show the influence of a very common condition in diabetes, namely, infection. Not every infection leads to a reduction of plasma cholesterol, but, in general, the plasma cholesterol is lower in infection than without infection. In table 7 are shown the average cholesterol values of 100 cases of diabetes with infection collected at *random* from our records by Dr. E. H. Bensley. They represent admission * values only. Admis-

* In all discussions hereafter, the term *admission* will apply to cholesterol data obtained when the patients were admitted to the clinic. Cholesterols obtained when the patients were discharged from the hospital will be referred to as *discharge* cholesterols. The term *discharge* cholesterol will also apply to data obtained from patients who were not admitted to the wards, but were treated in the out-patient clinic of the hospital. As a rule, such cholesterol determinations were made 14 days after institution of treatment. All data obtained subsequent to discharge from the wards, or after 14 days of out-patient treatment, will be referred to as *progress* cholesterols.

sion values of cases with infection are then compared with the averages of all admission data for the corresponding years. It will be observed that, with one exception (that is, 1929) the average admission cholesterols of the patients with infection were lower than the admission averages of all patients during the corresponding years.

The cases of infection shown in table 7 include individuals who had

TABLE VII

Influence of Infection upon Plasma Cholesterol *

	All Data		Acute Infection	
Year	No.	Average Cholesterol (Per Cent)	No.	Average Cholesterol (Per Cent)
1929	101	0.301	7	0.304
1930	207	0.282	31	0.184
1931	284	0.288	29	0.221
1932	216	0.263	33	0.167

* All data obtained on admission of patients to hospital.

received treatment previously and were admitted largely because of the infections. Previous treatment is obviously an influencing factor. These previously-treated cases are, therefore, excluded in table 8. Excluding the effects of previous treatment, it will be observed infection is still an impor-

TABLE VIII

Influence of Infection upon Plasma Cholesterol

	All Data		Acute Infection *	
Year	No.	Cholesterol † (Per Cent)	No.	Cholesterol † (Per Cent)
1929	101	0.301	5	0.319
1930	207	0.282	13	0.195
1931	284	0.288	19	0.196
1932	216	0.263	17	0.172

* Includes cases not treated previously.
† Data obtained on admission only.

tant factor influencing the interpretation of blood cholesterol. From these data, it is obvious that normal or low values found in such cases must not be attributed to improvement of treatment; the infection, per se, may have lowered the cholesterol.

While this paper was in preparation, there were two patients in the wards who strikingly showed the influence of two of the previously mentioned conditions, namely, hyperthyroidism (6377/34) and myxedema * (6275/34). In both cases, it was very difficult, for a time, to control the

* There are now three cases of this rare combination of conditions in this clinic.

diabetes. In spite of poor control, however, the plasma cholesterol was low in the case of *hyperthyroidism;* but following control of the hyperthyroidism (iodine and thyroidectomy, etc.) the cholesterol increased, reaching as high a level as 0.315 per cent; the diabetes was still very difficult to control. In the case of *hypothyroidism,* the cholesterol was as high as 0.396 per cent. This might have been due to the diabetes or the thyroid disease. Following thyroid extract medication, however, it *decreased.* Since treatment of the diabetes alone with diet and insulin had no effect, it appears reasonable to conclude that the excess cholesterol was due largely to the thyroid disease.

TABLE IX

Effects of Hyperthyroidism and Hypothyroidism upon Plasma Cholesterol in Diabetes Mellitus

Hosp. No. 6377/34 Diagnosis: Hyperthyroidism			Hosp. No. 6275/34 Diagnosis: Myxedema		
Date	Plasma Cholesterol (Per Cent)	Treatment	Date	Plasma Cholesterol (Per Cent)	Treatment
Nov. 6, 1934	0.163		Oct. 30, 1934	0.333	
10	0.177		Nov. 3	0.282	
12	0.181		9	0.264	
13	0.164		13	0.238	
20	0.181		14	0.228	
Dec. 7	0.185	Thyroid	16	0.273	
14	0.244	Lobectomy	19	0.208	
20	0.277	Thyroid	23	0.238	
22	0.179	Lobectomy	26	0.396	
28	0.228		Dec. 3	0.292	
31	0.308		5	0.297	
Jan. 2, 1935	0.315		7	0.264	
4	0.333		10	0.302	Thyroid extract
5	0.396		12	0.282	grs. v, b.i.d.
7	0.362		14	0.333	
			19	0.222	Thyroid extract
			21	0.252	grs. v, t.i.d.
			24	0.235	" b.i.d.
			26	0.228	
			28	0.185	
			31	0.177	
			Jan. 2, 1935	0.219	
			5	0.219	
			7	0.214	

A summary of the findings in these two cases is given in table 9. The data clearly demonstrate the possible influence of the metabolic effects of one condition upon another and the difficulties of interpretation of blood cholesterol. An analogy is found in a combination of typhoid fever and diabetic coma. In one of our cases (3620/32) when the patient was admitted to the hospital and, while in coma, there was the usual leukocytosis of diabetic coma; the white cell count was 32,700. Four days later, following com-

plete recovery from the coma, there was the leukopenia typical of typhoid fever; the cell count was 5,000.

In table 10 is shown the relationship found between plasma cholesterol and arteriosclerosis in 300 cases of diabetes selected at *random*. In this group, there were 166 cases of cardiovascular disease.* The average

TABLE X

Relationship between Plasma Cholesterol and Arteriosclerosis in 300 Diabetics Selected at Random

Group	Arterio-sclerosis	No.	M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
Whole	Present	166	217	91	4.72	8	6.15	1.3
	Absent	134	209	68	3.92			
Age 50 years and under	Present	57	213					
	Absent	84	213					
Over age 50 years	Present	109	219	72	4.68	16	9.35	1.7
	Absent	50	203	86	8.11			

M = Mean (average cholesterol—mg. per 100 c.c. plasma).
σ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

plasma cholesterol of the whole group was 0.213 per cent and it will be observed that, when the cases were grouped according to the presence or absence of vascular disease, a small difference only was found between the average cholesterols of the two groups, namely, 8 milligrams. That this difference was of little or no significance is shown by ratio of the difference to its probable error ($\Delta/PE\Delta = 1.3$).

Since a high incidence of cardiovascular disease is expected in elderly people even in nondiabetics, and since hypercholesterolemia has not been found in nondiabetic arteriosclerotics with the same frequency as in the diabetic with arteriosclerosis, it was considered important to exclude the effects of advanced age. The above mentioned 300 cases were, therefore, divided into two groups according to age, namely, (*a*) individuals of age 50 years and under and (*b*) those over age 50 years. The results of this grouping are shown in the same table. It will be noted that method of grouping did not affect the results; regardless of age, the average cholesterols of those with, and of those without, cardiovascular disease were approximately the same. In the younger age group, the average cholesterol of those with cardiovascular disease was identical with that of those with

* It is of interest to note that this incidence of cardiovascular disease, namely, 55.3 per cent, agrees very closely with that of a previously reported random selection. In the latter, the incidence was 62.6 per cent.[2]

no cardiovascular disease; and, according to the ratio of the difference to its probable error, the difference of cholesterol found in the older age group was not significant ($\Delta/PE\Delta = 1.7$).

The above findings fit in with the previously mentioned experiences of Hazel Hunt in Joslin's clinic.[24] Blood cholesterol values were not found high in arteriosclerosis. Nor was there any correlation between the degree of arteriosclerosis and hypercholesterolemia; the group which showed the lowest average blood cholesterol was the group which had the greatest degree of arteriosclerosis.

As stated, the selection of the above mentioned 300 cases was *random*. No attention was paid to the presence or absence of associated conditions which might have increased or decreased the blood cholesterol in these cases. Therefore, in view of previous observations, the possibility had to be considered that some of these diabetics may have had sufficient hypercholesterolemia for some time to have led to arteriosclerosis, but that, at the time these analyses were made, they may have suffered from infection or some other conditions which may have led to reduction of cholesterol. These 300 cases were, therefore, re-investigated and a variety of disturbing factors were found. There were, for example, 10 cases of hyperthyroidism. The average age of these 10 diabetics was 50.9 years and the average duration of the diabetes was 6.3 years. The average plasma cholesterol was practically normal, namely, 0.192 per cent. It was greater than 0.2 per cent in three cases only. Yet of these 10 individuals, two had retinal changes characteristic of arteriosclerosis and three had " senile " cataracts.

In view of the above findings, an attempt was made to collect a group of diabetics who either had no other disease or in whom there were no detectable associated conditions or complications other than cardiovascular disease. The selection was otherwise *random*. Among 1000 case records so examined, there were 167 only of such individuals and, among them, 62 were found with cardiovascular disease. A summary of the cholesterol findings in these 167 cases is shown in table 11.

Again, it will be observed that by simply dividing the cases according to the presence or absence of cardiovascular disease, there was no appreciable difference between the average cholesterol of the cases with, and of those without, vascular disease ($\Delta/PE\Delta = 0.69$). However, when the cases were grouped according to age, a definite difference was found; in the group of individuals of age 50 years and under, the average cholesterol of those with cardiovascular disease was 43 milligrams higher than in those without cardiovascular disease. Expressed as percentage difference, the average plasma cholesterol in the cases with cardiovascular disease was about 19 per cent higher than in the cases without cardiovascular disease. That the difference of 43 milligrams was significant is shown by the ratio of the difference to its probable error ($\Delta/PE\Delta = 3.5$). The finding in the older age group appears to be disturbing; the average cholesterol of those with no cardiovascular disease was 17 milligrams higher than the average of

TABLE XI

Relationship between Plasma Cholesterol and Arteriosclerosis in 167 Diabetics Selected at Random but with no Detectable Associated Conditions or Complications other than Cardiovascular Disease

Group	Arterio-sclerosis	No.	M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
Whole	Present	62	227	89	7.55	6	9.17	0.69
	Absent	105	221	78	5.22			
Age 50 years and under	Present	26	267	81	10.65	43	12.1	3.5
	Absent	68	224	73	5.89			
Over age 50 years	Present	36	198	93	10.35	17	14.3	1.2
	Absent	37	215	87	9.67			

M = Mean (average cholesterol—mg. per 100 c.c. plasma).
σ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

those with the disease. However, according to the ratio of the difference to its probable error, this finding is of little or no significance ($\Delta/PE\Delta = 1.2$). *Here, therefore, we find the first suggestion, statistically, of a causal relationship between hypercholesterolemia and cardiovascular disease.*

In the above study, no attention was paid to the presence or absence of *hypertension.* As stated previously, Mjassnikow [20] found an increase of blood cholesterol regularly in advanced arteriosclerosis. No such increase was, however, found in "essential" or nephritic hypertension. Since the atherosclerosis of diabetes is not generally associated with hypertension and since hypertension may, per se, lead to arteriosclerosis, it was considered important to group the 62 cases of cardiovascular disease according to the presence or absence of increase of blood pressure. A summary of the results is shown in table 12.

It will be observed that it was important to exclude hypertension, in order to determine the relationship between cardiovascular disease and blood cholesterol. By grouping these cases without regard to age, the average cholesterol of those with no hypertension was 35 milligrams higher than those with hypertension. Expressed as percentage difference, the average cholesterol of the cases with no hypertension was about 17 per cent higher than those with hypertension. That this difference of 35 milligrams was *probably* significant is suggested from the ratio of the difference to its probable error ($\Delta/PE\Delta = 2.3$).

The importance of excluding hypertension is more clearly shown in the same table where the cases are grouped with respect to age. It will be observed that, in the cases of hypertension, the average cholesterol of those

TABLE XII

Relationship between Plasma Cholesterol and Hypertension in the 62 Cases of Cardiovascular Disease Shown in Table 11

Group	No.	M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
Whole	62	227					
Hypertension	18	202	78	12.3	35	15.2	2.3
No hypertension	44	237	89	9.0			
Hypertension—Age 50 years and under	4	211	74	24.8	11	28.7	0.38
Over age 50 years	14	200	81	14.6			
No Hypertension—Age 50 years and under	22	270	94	13.4	66	17.4	3.8
Over age 50 years	22	204	78	11.1			

M = Mean (average cholesterol—mg. per 100 c.c. plasma).
σ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

of age 50 years and under was only 11 milligrams higher than that of the older age group and, according to the ratio of the difference to its probable error, this difference of 11 milligrams was not significant ($\Delta/PE\Delta = 0.38$). On the other hand, in the cases with no hypertension, there was a definite difference between the cholesterol values of the two age groups; the average cholesterol of the younger age group was 66 milligrams higher than that of the older age group and, according to the ratio of this difference to its probable error, the difference of 66 milligrams was significant ($\Delta/PE\Delta = 3.8$).

The intimate relationship between cardiovascular disease and blood cholesterol is more clearly shown in table 13. It will be observed that, when grouped without regard to age, the average cholesterol of those with cardiovascular disease was not appreciably greater than that of those with the disease; the difference was 16 milligrams only; and, according to the ratio of the difference to its probable error, this finding was not significant ($\Delta/PE\Delta = 1.5$). However, when the cases were grouped according to age, a definite relationship was found between cardiovascular disease and cholesterol in the younger age group of diabetics; the average cholesterol of those with cardiovascular disease was 46 milligrams higher than that of the group with no detectable vascular disease. Expressed as percentage difference, the average cholesterol in the cases with cardiovascular disease was about 20 per cent higher than in those in whom no vascular changes were found. That this difference of 46 milligrams was significant is shown by the ratio of the difference to its probable error ($\Delta/PE\Delta = 3.1$). In the older age group, it appeared that those with cardiovascular disease had

TABLE XIII

Relationship between Plasma Cholesterol and Cardiovascular Disease without Hypertension According to Age

Group	Arterio-sclerosis	No.	M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
Whole	Present	44	237	89	9.00	16	10.3	1.5
	Absent	105	221	78	5.12			
Age 50 years and under	Present	22	270	94	13.4	46	14.7	3.1
	Absent	68	224	73	5.96			
Over age 50 years	Present	22	204	78	11.1	11	14.8	0.74
	Absent	37	215	87	9.67			

M = Mean (average cholesterol—mg. per 100 c.c. plasma).
σ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

slightly lower cholesterol values than those without detectable changes; the average cholesterol of those without cardiovascular disease was about 6.4 per cent higher than those with the disease. Judging, however, by the ratio of the difference to its probable error, this finding was not significant ($\Delta/PE\Delta = 0.74$). Combining all of the above mentioned findings, therefore, and by weighting percentages, it appears reasonable to conclude that *there is an intimate association between cardiovascular disease and hypercholesterolemia.*

Parenthetically, the above data present another problem for solution in diabetes. The purpose of not including elderly diabetics and those with hypertension in this investigation was to exclude arteriosclerosis which is known to develop in the nondiabetic apparently irrespective of the cholesterol content of the blood. Since all of these patients were practically on the same type of diet, it was expected that the incidence of hypercholesterolemia among the elderly diabetics and those with hypertension would not be less than among the younger age group of patients. An artificial correlation between hypercholesterolemia and cardiovascular disease might, therefore, be found. The purpose of this study was to determine whether young diabetics with cardiovascular disease have more cholesterol in the blood than those without cardiovascular disease. The above data, therefore, support the view, statistically at least, that the metabolism of the young diabetic differs from that of elderly individuals with respect to lipoids. The data clearly show that excess accumulation of blood cholesterol is more marked in the young, than in the elderly, diabetic. The data, it should be observed, fit in with the previously mentioned observations of Klotz and Manning [8] namely, the association of fatty deposition in the intima with definite age

periods—its frequency between the ages of 20 to 30 years and its unusual occurrence after age 50 years. An analogy is suggested in the selective retention of vegetable pigments; why some diabetics are more prone than others to xanthosis (carotinemia) is, as yet, not known.

Effect of High Carbohydrate-Low Calorie Diet

The conclusion that there is a causal relationship between the level of circulating cholesterol and arteriosclerosis is statistical, and is supported by a large number of observations. Other experiences, however, also lend themselves to similar treatment. The following were data obtained with the high carbohydrate-low calorie diet.

A variety of metabolic effects of the high carbohydrate-low calorie diet in diabetes used in this clinic were discussed elsewhere[49, 50, 51] and will, therefore, not be dealt with here. At present, we are concerned with one observation only, namely, the effects of this diet upon blood cholesterol. As I pointed out previously, one of the most striking effects is the immediate and sustained decrease of plasma cholesterol. Of the first 500 cholesterol determinations, 393 (78.6 per cent) were under 0.2 per cent and 199 (39.8 per cent) were no greater than 0.15 per cent. The low values were sufficiently striking to prompt Dr. Joslin * to ask "What would happen if the cholesterol dropped below the normal. Is there any danger?" A more detailed analysis of the cholesterol data with this diet is shown in the following tables:

Table XIV

Immediate Effect of Treatment upon Plasma Cholesterol

	Admission Data		Discharge Data *	
Year	No.	Average Cholesterol (Per Cent)	No.	Average Cholesterol (Per Cent)
1926	62	0.348	41	0.284
1927	43	0.354	26	0.262
1928	59	0.325	48	0.276
1929	101	0.301	82	0.241
1930	207	0.282	135	0.253
1931	284	0.288	146	0.212
1932	216	0.263	127	0.205
1933	187	0.242	111	0.182

* Includes cases only in which cholesterol data were obtained before treatment commenced. Includes non-ward cases, two weeks after commencement of treatment. (Average duration of hospital treatment 14 days.)

In table 14 are shown the *immediate* effects of treatment with the high carbohydrate-low calorie diet compared with those of the older and relatively low carbohydrate-high fat diets. In this table are recorded annual average blood cholesterols when the patients were first admitted to the clinic and.

* Personal communication.

again, about two weeks later. It will be observed that in 1931 and 1932, that is, when practically every new patient with advanced diabetes was given the high carbohydrate-low calorie diet, the average *discharge* cholesterol was nearly normal. In 1933, the average *discharge* cholesterol was normal. These data alone, however, do not show the effects of this diet very clearly. According to weighted averages, the average reduction of plasma cholesterol during the period 1931–1933 was not very much greater than those found during the period of high fat feeding 1926–1930; with the latter diets, the average reduction for the period 1926–1930 was about 48 milligrams, whereas, with the new diet it was about 65 milligrams. It should, however, be observed that in this comparison of *admission* with *discharge* data, conditions which may influence plasma cholesterol levels other than diet were not excluded. Also, as was previously shown (table 6) the initial level of plasma cholesterol may alone influence the *rate* at which the cholesterol returns to the normal level and it will be observed that the *admission* values prior to 1931 were higher than in the following years.

TABLE XV

Immediate Effects of Treatment with Different Diets upon Plasma Cholesterol

High Carbohydrate-Low Calorie Diet				Low Carbohydrate-High Fat Diet			
Hosp. No.	Cholesterol (Per Cent)			Hosp. No.	Cholesterol (Per Cent)		
	Admission	Discharge	Difference		Admission	Discharge	Difference
2404–32	0.347	0.113	−0.234	46–29	0.326	0.463	+0.137
3257	0.333	0.196	−0.137	254	0.302	0.326	+0.024
3553	0.362	0.208	−0.154	431	0.340	0.427	+0.087
5779	0.302	0.302	——	1388	0.396	0.302	−0.094
6864	0.308	0.260	−0.048	3761	0.370	0.406	+0.036
7125	0.362	0.175	−0.187	5617	0.321	0.225	−0.096
7193	0.333	0.214	−0.119	3805–28	0.387	0.314	−0.073
1103–33	0.333	0.185	−0.148	6017	0.333	0.225	−0.108
1630	0.333	0.171	−0.162	6771	0.302	0.268	−0.034
1835	0.326	0.260	−0.066	6870	0.300	0.260	−0.040
4991	0.378	0.192	−0.186	7218	0.333	0.277	−0.056
5326	0.302	0.216	−0.086	7092	0.300	0.347	+0.047
Average	0.335	0.207	0.128	Average	0.334	0.320	0.014

In table 15, are shown 24 cases carefully selected with respect to the level of the blood cholesterol prior to treatment. The data of the two types of diets are also otherwise reasonably comparable. It will be observed that, with the new diet, the average *immediate* reduction of cholesterol was 128 milligrams per 100 c.c. plasma and that the diet failed to lower the plasma cholesterol in one case (5779/32) only; whereas, with the older diets, the average reduction was only 14 milligrams. Of these 12 cases, there was no reduction in five instances; the cholesterol was not only reduced, but slightly

TABLE XVI

Influence of Treatment upon Plasma Cholesterol
(Progress data only; data obtained before and immediately after (14 days) treatment not included)

	A		*B*		*C*		*D*		*E*		High Carbohydrate		Restricted Carbohydrate		All Data	
	No.	Chol. %	No.	Chol. %	No.	Chol. %	No.	Chol. %	No.	Chol. %	No.	Chol. %	No.	Chol. %	No.	Chol. %
1926	82	0.251	64	0.241	18	0.226	10	0.230	4	0.282			16	0.217	194	0.242
1927	221	0.245	102	0.228	31	0.248	86	0.216	37	0.264			24	0.232	501	0.237
1928	222	0.308	48	0.230	12	0.232	42	0.182	24	0.246			43	0.205	391	0.267
1929	67	0.303	31	0.226	42	0.200	75	0.230	16	0.232			27	0.228	258	0.243
1930	17	0.249	12	0.232	28	0.241	64	0.218	5	0.254	586	0.178	38	0.208	750	0.188
1931	13	0.258	3	0.272	6	0.229	30	0.232	14	0.243	422	0.194	18	0.202	506	0.201
1932	12	0.272	4	0.315	9	0.242	6	0.228	3	0.261	313	0.172	32	0.209	379	0.183
1933	6	0.268	2	0.364	4	0.231	23	0.202	1	0.282	235	0.186	26	0.218	297	0.192
	640	0.275	266	0.234	150	0.228	336	0.216	104	0.252	1556	0.181	224	0.214	3276	

higher than on admission. We have never been able to explain the temporary increase of cholesterol in some cases shortly after commencement of treatment. Such increases are occasionally seen with the new diet also.

The *progress* data, that is, the data obtained after the patients had been on the diet for many weeks, months and years, demonstrated more clearly the effects of the high carbohydrate-low calorie diet on blood cholesterol. A summary of our experiences is shown in table 16. Averages of plasma cholesterol with the new diet are compared with those found with the old A, B, C, D and E diets, the corresponding carbohydrate values of which were 50, 75, 100, 125 and 150 grams respectively. In these old diets, the fat content ranged between 140 and 150 grams. It will be observed that, with all of the high fat diets, the average cholesterol values were high, regardless of their carbohydrate contents; the average of 104 determinations with Diet E (0.252 per cent) the carbohydrate content of which was 150 grams, was not very much lower than the average of 640 determinations with Diet A (0.275 per cent) the carbohydrate content of which was 50 grams only. The findings with these old diets contrast markedly with the cholesterol values obtained with the high carbohydrate-low calorie diet. It will be observed that the average of 1556 determinations of *progress* cholesterol with this diet was only 0.181 per cent. Attention is, again, drawn to the fact that these are *progress* data, that is, cholesterol determinations made after the patients were on the high carbohydrate-low calorie diet for many weeks, months, and years. They clearly indicate the *sustained* decrease of plasma cholesterol with the new diet.

Parenthetically, the *progress* data obtained with the "restricted carbohydrate diet," also shown in the above table, are of interest. In the past, this diet was generally given to individuals with no clinical signs or symptoms of diabetes other than the glycosuria; in whom the glycosuria was discovered accidentally and whose blood sugars were normal in the fasting state. This "restricted carbohydrate diet" included avoiding sugar in tea and coffee; pastries, puddings, cake and candy of all kinds; restriction of bread intake to about one slice (one ounce) at each meal and regulation of the total intake of food so as to keep the body weight slightly below the normal for the height and age. It will be observed that the *progress* cholesterols are not as satisfactory as with the high carbohydrate-low calorie diet; of 224 determinations, the average cholesterol was 0.214 per cent. In view of these experiences, treatment of such individuals obviously requires modification; the diets of these individuals were apparently still too high with respect to fat. The case shown in table 17 is cited as a typical example of the course of events when the high carbohydrate-low calorie diet was substituted for the older forms of treatment. The data include 46 cholesterol determinations during a period of about six years. They clearly show the *sustained* decrease of plasma cholesterol with the high carbohydrate-low calorie diet.

TABLE XVII

Effects of Substitution of High Carbohydrate-Low Calorie Diet for Liberal Carbohydrate-High Fat Diet upon Plasma Cholesterol
(Hosp. No. 5053/28)

Date	Plasma Cholesterol (%)	Diet			Insulin	Date	Plasma Cholesterol (%)	Diet			Insulin
		C	F	P				C	F	P	
Aug. 25, 1928	0.236	150	150	60	20/ 0/20	April 2, 1931	0.241	254	56	72	20/0/20
Oct. 26	0.241	"	"	"	"	May 14	0.166	"	"	"	"
Nov. 16	0.260	"	"	"	"	July 7	0.184	"	"	"	"
Dec. 15	0.282	"	"	"	"	Aug. 6	0.125	"	"	"	"
Jan. 11, 1929	0.340	"	"	"	"	Sept. 15	0.122	"	"	"	"
Febr. 8	0.315	"	"	"	"	Oct. 24	0.166	"	"	"	"
March 8	0.273	"	"	"	"	Nov. 17	0.166	"	"	"	"
April 5	0.396	"	"	"	20/10/20	Jan. 13, 1932	0.156	"	"	"	"
May 29	0.232	"	"	"	"	Febr. 23	0.169	"	"	"	"
June 27	0.285	"	"	"	"	April 25	0.228	"	"	"	"
July 30	0.254	"	"	"	"	June 22	0.287	"	"	"	"
Aug. 27	0.242	"	"	"	"	Aug. 27	0.111	"	"	"	"
Oct. 28	0.216	"	"	"	"	Dec. 2	0.196	"	"	"	"
Dec. 26	0.321	"	"	"	"	March 6, 1934	0.185	"	"	"	"
Jan. 16, 1930	0.277	"	"	"	"	April 28	0.238	"	"	"	"
March 7	0.252	218	56	69	"	July 24	0.208	"	"	"	"
June 11	0.120	236	"	72	"	Oct. 24	0.163	"	"	"	"
July 2	0.145	254	"	"	20/ 0/20	Nov. 7	0.238	"	"	"	"
Sept. 4	0.139	"	"	"	"	Jan. 3, 1934	0.238	"	"	"	"
Oct. 2	0.111	"	"	"	"	Febr. 1	0.181	"	"	"	"
Nov. 7	0.111	"	"	"	"	March 15	0.214	"	"	"	"
Dec. 30	0.160	"	"	"	"	July 24	0.200	"	"	"	"
Febr. 5, 1931	0.117	"	"	"	"	Dec. 19	0.204	"	"	"	"

DOES THE HIGH CARBOHYDRATE-LOW CALORIE DIET PREVENT, OR DELAY THE DEVELOPMENT OF, ARTERIOSCLEROSIS?

The proof that there is an intimate association between hypercholesterolemia and arteriosclerosis appears to be definite. It, therefore, appears reasonable that if the relationship between the two conditions is causal, the high carbohydrate-low calorie diet (or any other condition which can keep the cholesterol content of the blood at the proper level) should prevent, or at least delay development of, arteriosclerosis. An attempt was, therefore, made to determine whether the incidence of cardiovascular disease among diabetics treated with the high carbohydrate-low calorie diet was lower than among diabetics treated otherwise.

It is of interest here to note that other conditions commonly associated with hypercholesterolemia and with cardiovascular disease have largely disappeared in our clinic with the institution of this diet. Xanthosis (carotinemia) is now rare. We have had three cases only during the last five years. The significance of carotinemia and its relationship to arteriosclerosis were discussed elsewhere.[37, 38] Gangrene is also disappearing. Since 1931, we have had 36 cases, but, in 25, the gangrene was present when the patients were first admitted to the Clinic. Therefore, 11 only of our own patients were found to have developed gangrene during this period and, *without exception*, every one of these patients failed to follow treatment. This experience fits in with a fact well established with the older diets, namely, that it is the uncontrolled diabetic who is particularly susceptible to this complication.

The beneficial results with the high carbohydrate-low calorie diet in another cardiovascular disturbance, namely, coronary disease, were discussed elsewhere.[51] Our findings, clinically, and according to the electrocardiographic tracings, have been at times striking. We are not alone in this experience. Poulton [52] reported somewhat similar results. The explanation is not clear. My first impression was that improvement was due to supplying the heart muscle with that food which is essential for normal function, namely, glycogen. This would fit in with the suggestion made by Klotz that the media of the artery in a diabetic may degenerate prematurely because of lack of glycogen. Are the beneficial results due to reduction of lipoids in the intima? Does reduction of lipoids lead to more patent coronary arteries? The observations of Labbé and Heitz [10] and of McMeans and Klotz [53] are of interest here. According to Labbé and Heitz [10] deposition of cholesterol in the intima leads to obliteration of arteries, and McMeans and Klotz [53] have found that lipoid deposits produced in the aorta of rabbits by feeding cholesterol *disappear* if the cholesterol is discontinued for several weeks.

Method of Investigation. In order to determine whether the high carbohydrate-low calorie diet can prevent, or at least delay development of, arteriosclerosis, 50 diabetics who were treated with this diet were investigated. The cases were carefully selected with respect to the condition of the cardiovascular system; when these 50 patients were first given the new diet, they had no signs of arteriosclerosis according to (*a*) careful physical examination, (*b*) examination of the fundi, (*c*) roentgen-ray examination of the vessels of the lower extremities for calcification and (*d*) roentgen-ray examination of the heart (six foot plate).

Though, as stated, the juvenile diabetic apparently develops arteriosclerosis as readily as the adult, children were not included in this study. Since liability to arteriosclerosis increases with age even in nondiabetics, and since we are particularly concerned with arteriosclerosis in the young diabetic, all individuals past age 50 years were also excluded. A summary of the cases selected with respect to age, duration of diabetes, and severity of diabetes is shown in table 18. It will be observed that the maximum, minimum and average ages were 49, 29, 43.8 years respectively. The maximum, minimum and average durations of the diabetes were 8.3, 4.5 and 5.6 years respectively. Of these 50 diabetics, 16 required insulin and, in 34 cases, the diabetes could be controlled by diet alone. Different degrees of severity of diabetes were, therefore, also included.

Of these 50 individuals, arteriosclerotic changes were detected in 14 only, an incidence of 28 per cent. This incidence, it will be noted, is remarkably low when compared with our experiences with the older diets. In a similar age group of individuals and, according to the same methods of examination, cardiovascular disease was found in 55 per cent of the cases.[2] In calculating this percentage, however, no consideration was given to *duration* of the diabetes. The beneficial effects of the high carbohydrate-low calorie diet

TABLE XVIII

Summary 1

Number of cases		50
Age: Maximum	49	
Minimum	29	
Average	43.8	
Duration of diabetes: Maximum	8.3	
Minimum	4.5	
Average	5.6	
Insulin		16
No insulin		34
Arteriosclerosis		14

are more clearly shown when consideration is given to the *durations of the diabetes.* As stated previously, very few diabetics, *regardless of age,* were found in the past to have escaped vascular disease when they had diabetes for five years or more; according to postmortem findings [3] none escaped. In our previous study [2] of 81 individuals of 50 years of age and under who had diabetes for *five years or more, 69—an incidence of about 85 per cent*—had vascular disease; and even when the duration of the diabetes was less than five years, of 162 individuals of the same age group, 74—an incidence of about 40 per cent—were found to have vascular disease.

TABLE XIX

Relationship between Duration of Diabetes and Development of Arteriosclerosis

Duration of Diabetes (Years)	Number of Cases	Arteriosclerosis	
		Present	Absent
4.0–4.5	13	2	11
4.6–5.0	9	1	8
5.1–5.5	10	3	7
5.6–6.0	6	3	3
6.1–6.5	1	0	1
6.6–7.0	5	1	4
7.1–7.5	3	2	1
7.6–8.0	1	0	1
8.1–8.5	2	2	0

In table 19 is shown in more detail the relationship found between duration of diabetes and development of cardiovascular disease in this group of 50 cases. It will be observed that of 28 individuals with the diabetes of more than five years' duration, cardiovascular disease was detected in only 11—an incidence of approximately 39.3 per cent; that is, less than one-half the incidence which was found among our control cases of a similar age group.[2] It will be shown, however, presently that even this relatively low incidence can probably be lowered with proper attention to diet. Also significant appears to be the fact that some of these diabetics were treated with the older diets for periods ranging from six months to more than three years, *before* they were given the high carbohydrate-low calorie diet. In some, the blood cholesterol was not very high with the older diets. The data,

however, clearly show that a number of these patients were exposed to excess quantities of blood cholesterol for some time. Space does not permit citation of all the cases. The data in tables 20 and 21 are illustrative. It will be observed that in one case (table 20) the patient was on the older type of diet for about 10 months before the high carbohydrate-low calorie diet was given and in the other case (table 21) the older type of diet was in use for about four years. Incidentally, in the case shown in table 17, the patient

TABLE XX

Duration of Diabetes and Degree of Hypercholesterolemia before and since Treatment with High Carbohydrate-Low Calorie Diet
(Hosp. No. 6000/29. No arteriosclerosis)

Date	Plasma Cholesterol (%)	Date	Plasma Cholesterol (%)
Oct. 30, 1929	0.232 *	Oct. 18, 1930	0.109
Nov. 9	0.370	Nov. 22	0.185
16	0.427	Sept. 18, 1931	0.134
23	0.387	Dec. 24	0.228
30	0.308	March 26, 1932	0.138
Dec. 14	0.362	Oct. 1	0.143
28	0.333	Nov. 15	0.138
Jan. 25, 1930	0.256	Dec. 17	0.154
March 1	0.238	Jan. 21, 1933	0.164
15	0.228	Aug. 26	0.222
June 28	0.326	Oct. 2	0.151
Aug. 1	0.387 †	Jan. 27, 1934	0.187
Sept. 2	0.315	April 28	0.277
20	0.235	May 30	0.137

* Low carbohydrate diet.
† High carbohydrate diet.

TABLE XXI

Duration of Diabetes and Degree of Hypercholesterolemia before and since Treatment with High Carbohydrate-Low Calorie Diet
(Hosp. No. 2044/26. No arteriosclerosis)

Date	Plasma Cholesterol (%)	Date	Plasma Cholesterol (%)
April 28, 1926	*	June 20, 1930	0.222
Nov. 13	0.387	July 26	0.227
21	0.302	Aug. 23	0.177
23	0.302	Oct. 15	0.232
Jan. 19, 1929	0.347	Nov. 22	0.285
Febr. 2	0.222	March 21, 1931	0.238
16	0.354	July 4	0.208
March 30	0.321	Dec. 12	0.200
May 11	0.427	Jan. 6, 1932	0.157
June 29	0.302	May 6	0.185
July 20	0.370	June 7	0.173
Dec. 14	0.378	Febr. 1, 1933	0.315
March 15, 1930	0.268	April 15	0.208
May 17	†	Sept. 1	0.174
31	0.244	Dec. 9	0.214

* Low carbohydrate diet.
† High carbohydrate diet.

was on the older type of diet for about 17 months before the new diet was given. In all three tables, the data clearly show that these patients were exposed, for some time, to excess quantities of blood cholesterol before they were given the new diet. In spite of such exposures, however, none of these three individuals had any signs of cardiovascular disease when last examined, though all had diabetes for more than five years. It would thus appear that the high carbohydrate-low calorie diet protected them from this disease in spite of previous treatment. This fits in with the previously mentioned findings of McMeans and Klotz [53] namely, the disappearance of lipoid deposits in the aortae of rabbits when cholesterol feeding was discontinued.

Assuming that the high carbohydrate-low calorie diet was responsible for the low incidence of arteriosclerosis in this group of cases, an attempt was made to find the cause of the arteriosclerosis in those who developed it. As will presently be seen, excess blood cholesterol again appears to have been an influencing factor.

Duration of diabetes alone is not *entirely* excluded. This is shown in table 22; the average duration of the disease in the cases with cardiovascular disease was slightly greater than in those without vascular disease. The difference, however, appears to be small and, as will presently be shown, was not an important factor.

Severity of diabetes was considered. The data in table 22 suggest that

TABLE XXII

Summary 2

	Arteriosclerosis	No Arteriosclerosis
Number	14	36
Average age (years)	46.9	42.6
Insulin (No.)	5	11
No insulin (No.)	9	25
Duration of diabetes (years)	6.05	5.42

this was not a very important factor; it will be observed that of the 16 individuals who required insulin, five were found to have developed arteriosclerosis—an incidence of 31.2 per cent—and of the 34 individuals in whom the diabetes could be controlled by diet alone, arteriosclerosis was detected in nine—an incidence of 26.5 per cent. In view of the small number of observations, limited significance can be attached to the differences noted between these percentages. Incidentally, the data suggest that insulin, per se, does not appreciably protect the diabetic against arteriosclerosis. Joslin has stressed the importance of insulin in children. No child, he states, treated with insulin from the onset of the diabetes was found to have arteriosclerosis.[54] According to our data, however, as I shall presently show, it would appear that it is not the insulin, per se, which protects the diabetic from premature arteriosclerosis, but the control of the diabetes; the diabetic

under good control with diet alone is no more liable to arteriosclerosis than the one who requires insulin to control the disease.

Since neither duration of the diabetes nor severity of the disease appeared to account alone for the arteriosclerosis in the 14 cases, an attempt was made to estimate the *control* of the diabetes. As previously stated, Shepardson found, and it has been a fairly general impression for some time, that the uncontrolled diabetic is particularly susceptible to arteriosclerosis. An impression, however, is not proof; and a difficulty was at once encountered, namely, the absence of a reasonably reliable quantitative index of control. Such arbitrary terms as *poor, fair, good,* etc. are not satisfactory. The same term used in any two clinics may not be, and as a rule is not, strictly comparable. In one of our previous studies of blood cholesterol, control of diabetes was judged by frequency of glycosuria.[22] This index, however, could not be applied to this study since, with the disease of long duration (years) very few diabetics examine their urines with the necessary frequency. The following standard was, therefore, devised. It will be observed that, with it, data of different clinics are reasonably comparable. Though it is a very approximate index only of control, its simplicity recommends it. It is, at least in my opinion, more quantitative than any standard used hitherto. Degree of control of diabetes was rated as follows:

Rating	Laboratory Findings
0	Fasting blood sugar higher than 0.18 per cent; glycosuria in the fasting state and acetonuria.
1	Glycosuria in the fasting state, but no acetonuria; or, in the absence of glycosuria, a fasting blood sugar higher than 0.18 per cent.
2	Fasting blood sugar higher than normal, but less than 0.18 per cent.
3	Fasting blood sugar normal.

The following case taken at random from our records is cited as an example of the calculations:

	Urine sugar	Urine acetone	Blood sugar per cent	Control Index
Jan. 27, 1933	+	0	0.232	1
March 1	0	0	0.166	2
June 14	0	0	0.145	2
Sept. 3	0	0	0.240	1
Dec. 2	0	0	0.108	3
May 4, 1934	0	0	0.087	3
July 8	0	0	0.171	2
Aug. 14	+	tr	0.263	0
Aug. 21	0	0	0.133	2
Nov. 3	0	0	0.111	3
			Average:	1.90

It will be observed that of 10 examinations in this case, the average control index was 1.90. This value, it should be noted, closely approximates conditions described above under rating No. 2. In other words, a rating of 1.9 implies that, as a rule, the patient was exposed to mild hyperglycemia only; glycosuria and marked hyperglycemia were uncommon. Acetonuria

must have been very uncommon. This, it will be noted, fits in, in general, with the actual data. The reliability of this method of measuring control of diabetes was, however, tested in the following manner:

In a previous investigation [22] the cholesterol content of the blood plasma was found to be a reliable indication of the control of the diabetes. In order, therefore, to test the reliability of the control index, *average* control index was compared with *average* plasma cholesterol. A summary of 938 observations in 200 cases of diabetes is shown in table 23. The averages are graphically recorded in chart 2.

TABLE XXIII
Relationship between Control Index and Plasma Cholesterol

(938 observations on 200 diabetics)

Group	Control Index (Range)	Number of Cases	Plasma Cholesterol					
			M	ρ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
1	–1.00	23	244*	24.2	3.37			
						5	5.3	0.96
2	1.01–1.50	34	239	36.5	4.13			
						17	6.3	2.7
3	1.51–2.00	39	222	44.8	4.82			
						24	5.7	4.2
4	2.01–2.50	64	198	37.3	3.10			
						7	5.3	1.3
5	2.51–3.00	40	191	40.3	4.28			
A	–1.00	23	244	24.2	3.37			
						22	5.9	3.7
B	1.51–2.00	39	222	44.8	4.82			
						31	6.4	4.8
C	2.51–3.00	40	191	40.3	4.28			

* Milligrams per 100 c.c. plasma.
M = Mean.
ρ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

It will be observed that the 200 cases are grouped according to the control index; and that in comparing differences of cholesterol among the different groups, the significance of each difference is judged by its probable error. Assuming that when the ratio of a difference to its probable error is less than 3, little or no significance is to be attached to the difference, no significant relationship was found between the control index and plasma cholesterol when the ranges used in grouping the cases, according to the control index, were narrow. A significant difference of cholesterol was found between two groups only, namely, between Groups 3 and 4 ($\Delta/PE\Delta = 4.2$). However, when wider ranges of the control index were used, a definite re-

lationship was found between control index and plasma cholesterol. It will be observed that by comparing Group A with Group B the ratio of the difference to its probable error was 3.7 and with Groups B and C it was 4.8. As will presently be shown, however, the above data, alone, do not properly reflect the reliability of the control index.

The above mentioned 200 cases were selected at random. In view,

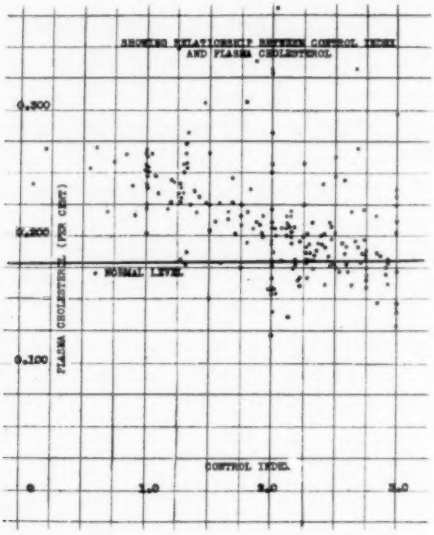


CHART 2

therefore, of the variety of conditions which may influence the level of the circulating cholesterol other than control of the diabetes, this method of estimating control of diabetes was reinvestigated and, in this investigation, cases which were found to have associated conditions or complications which could have influenced the cholesterol values were excluded. The results are summarized in table 24, and graphically recorded in chart 3. It will be observed that, by excluding conditions known to influence blood cholesterol other than the diabetes, a more definite relationship was found between control index and plasma cholesterol. (It may here be observed that a perfect correlation was not expected, since plasma cholesterol is, per se, not a perfect index of control of diabetes. Its use is, however, justified; the finding that blood cholesterol is a reliable index of the control of diabetes is statistically established.)

In previous studies, neither White and Hunt [25] nor I [38] were able to find a relationship between the height of blood sugar and the concentration of blood cholesterol. A priori, therefore, it would appear that no relationship should be found between control index and plasma cholesterol, since the control index is based to some extent upon blood sugar findings. Since a definite relationship was found, the discrepancy must be more apparent than

TABLE XXIV

Relationship between Control Index and Plasma Cholesterol in Uncomplicated Diabetes

(1037 observations on 187 diabetics)

Group	Control Index (Range)	Number of Cases	Plasma Cholesterol					
			M	ρ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
1	–1.00	23	277	58	8.10			
						24	9.8	2.4
2	1.01–1.50	27	253	43	5.54			
						25	6.6	3.8
3	1.51–2.00	40	228	34	3.60			
						18	4.9	3.7
4	2.01–2.50	45	210	34	3.30			
						29	5.8	5.0
5	2.51–3.00	52	181	51	4.73			
A	–1.00	23	277	58	8.10			
						49	8.9	5.5
B	1.51–2.00	40	228	34	3.60			
						47	5.9	7.9
C	2.51–3.00	52	181	51	4.73			

* Milligrams per 100 c.c. plasma.
M = Mean.
ρ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

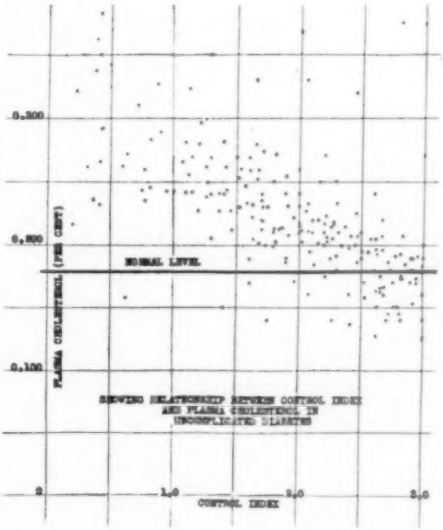


CHART 3

real. The explanation of the parallelism between the control index and plasma cholesterol is found in the method of calculating the control index. It should be observed [25, 38] that in the attempt to relate blood sugar to blood cholesterol, *level* of cholesterol was compared with actual *level* of blood sugar; whereas, in calculating the control index, control of the diabetes is judged more by the *persistence* of high or low levels of blood sugar than by actual height; a blood sugar of 0.2 per cent, for example, has the same significance as a blood sugar of 0.3 per cent.

TABLE XXV
Control of Diabetes

Group	No.	Number of Visits	Control Index
Whole	50	819	1.94
With arteriosclerosis	14	253	1.53
No arteriosclerosis	36	566	2.12

In table 25 is shown the relationship found between the control index and cardiovascular disease in the 50 cases investigated. It will be observed that of 253 examinations in the 14 cases with cardiovascular disease, the average control index was 1.53; whereas, of 566 examinations in the 36 cases with no cardiovascular disease, the average control index was 2.12. Therefore, from these data alone, it would appear that poor control of the diabetes was an important cause of the cardiovascular disease in these 14 cases. It should be observed that a control index of 1.53 implies, according to the above mentioned method of rating, that, as a rule, the patient was exposed to marked hyperglycemia; the blood sugar, as a rule, was higher than 0.18 per cent. Glycosuria was also frequent.

TABLE XXVI
Control of Diabetes

Group	Arteriosclerosis							No Arteriosclerosis						
	No.	Visits	Control of Diabetes					No.	Visits	Control of Diabetes				
			0	1	2	3	A.M.			0	1	2	3	A.M.
Whole	14	253	9	129	87	28	1.53	36	566	6	71	338	151	2.12
Insulin	5	121	6	71	35	9	1.41	11	206	3	52	122	29	1.86
No insulin	9	132	3	58	52	19	1.66	25	360	3	19	216	121	2.26

It is obviously more difficult to control the diabetes when it is severe than when it is mild. Therefore, in order to measure the effects of severity of the diabetes, the cases were regrouped and the average control index of the insulin-treated cases was compared with the average control index of the in-

dividuals in whom the diabetes could be controlled by diet alone. A summary of the findings is shown in table 26. It will be observed that severity of the diabetes was to some extent an influencing factor; in both groups, the average control index of the insulin-treated cases was somewhat lower than that of the individuals in whom the diabetes could be controlled by diet alone. The data, however, also show that, *regardless of the severity of the disease,* the average control index of those with cardiovascular disease was lower than in the group of cases with no cardiovascular disease. These findings, therefore, fit in with and tend to confirm the previous observation that severity of diabetes does not alone explain the development of the cardiovascular disease in these cases. They also support another observation made previously, namely, that insulin, per se, does not protect the diabetic against cardiovascular disease.

TABLE XXVII

Relationship between Plasma Cholesterol and Cardiovascular Disease in 50 Diabetics Treated with the High Carbohydrate-Low Calorie Diet

Group	No.	Plasma Cholesterol					
		M	ρ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
Whole	819	202					
Cardiovascular disease	253	220	76	3.18	25	4.1	6.1
No cardiovascular disease	566	195	89	2.59			

M = Mean.
ρ = Standard deviation.
PEm = Probable error of mean.
Δ = Difference between means.
PEΔ = Probable error of difference.

Table 27 shows the relationship found between plasma cholesterol and cardiovascular disease in this group of 50 cases. The data fit in with the previous studies (see table 13). It will be observed that the average plasma cholesterol in the cases with cardiovascular disease was higher than among the individuals with no detectable vascular disturbances; of 253 tests among the arteriosclerotics, the average cholesterol was 0.22 per cent; whereas, of 566 tests among those with no detectable signs of arteriosclerosis, the average cholesterol was 0.195 per cent only. The difference between the two groups is not very great, namely, 25 milligrams; but the ratio of the difference to its probable error (6.1) clearly indicates that the difference was significant.

Table 28 shows the relationship found between the control index and plasma cholesterol in these 50 cases grouped according to severity of the disease. Both control index and cholesterol also clearly show the relation-

TABLE XXVIII

Relationship between Control Index and Plasma Cholesterol in 50 Diabetics Treated with High Carbohydrate-Low Calorie Diet
(Effects of insulin)

Group	Arteriosclerosis				No Arteriosclerosis			
	Number of Cases	Number of Visits	Control Index	Cholesterol (%)	Number of Cases	Number of Visits	Control Index	Cholesterol (%)
Whole	14	253	1.53	0.220	36	566	1.86	0.195
Insulin	5	121	1.41	0.228	11	206	2.26	0.201
No insulin	9	132	1.66	0.204	25	360	2.12	0.191

ship between control of the diabetes and development of cardiovascular disease. It will be observed that the average cholesterol was higher and the average control index was lower among those with cardiovascular disease and among those in whom there were no signs of cardiovascular disease. This applied to the insulin-treated cases as well as to those in whom the diabetes could be controlled by diet alone. Since in the selection of these cases, care was taken to exclude conditions which are known to affect blood cholesterol, the higher average of cholesterol found among the cases with cardiovascular disease is reasonably attributed to dietary irregularities.

Tables 29 and 30 show the relationship between control of diabetes, plasma cholesterol, duration of diabetes and arteriosclerosis. The data

TABLE XXIX

Relationship between Degree of Control of Diabetes, Duration of Diabetes and Development of Arteriosclerosis

Duration of Diabetes (Years)	Arteriosclerosis							No Arteriosclerosis						
	Number of Cases	Control of Diabetes						Number of Cases	Control of Diabetes					
		Number of Tests	0	1	2	3	M		Number of Tests	0	1	2	3	M
4.0–4.5	2	36	4	3	27	2	1.75	11	132	2	18	88	24	2.01
4.6–5.0	1	13	0	8	4	1	1.46	8	126	0	13	66	47	2.26
5.1–5.5	3	38	1	19	13	5	1.56	7	122	2	11	68	41	2.21
5.6–6.0	3	46	0	24	19	3	1.54	3	51	0	13	27	11	1.96
6.1–6.5								1	17	0	2	7	8	2.35
6.6–7.0	1	20	1	14	2	3	1.35	4	73	1	9	51	12	2.01
7.1–7.5	2	63	2	42	8	11	1.44	1	26	0	3	17	6	2.11
7.6–8.0								1	19	1	2	14	2	1.90
8.1–8.5	2	37	1	19	14	3	1.51							
Summary	14	253	9	129	87	28	1.53	36	566	6	71	338	151	2.12

TABLE XXX

Relationship between Plasma Cholesterol, Duration of Diabetes and Development of Arteriosclerosis

Duration of Diabetes (Years)	Arteriosclerosis					No Arteriosclerosis				
	Number of Cases	Plasma Cholesterol (Per Cent)				Number of Cases	Plasma Cholesterol (Per Cent)			
		Number of Tests	Maximum	Minimum	Average		Number of Tests	Maximum	Minimum	Average
4.0–4.5	2	36	0.241	0.151	0.212	11	132	0.277	0.111	0.201
4.6–5.0	1	13	0.189	0.111	0.198	8	126	0.297	0.120	0.189
5.1–5.5	3	38	0.315	0.124	0.229	7	122	0.333	0.133	0.193
5.6–6.0	3	46	0.252	0.133	0.234	3	51	0.252	0.166	0.187
6.1–6.5						1	17	0.241	0.141	0.198
6.6–7.0	1	20	0.244	0.181	0.230	4	73	0.282	0.132	0.200
7.1–7.5	2	63	0.333	0.171	0.215	1	26	0.264	0.154	0.213
7.6–8.0						1	19	0.222	0.100	0.202
8.1–8.5	2	37	0.268	0.159	0.224					
Summary	14	253	0.333	0.111	0.220	36	566	0.333	0.100	0.195

clearly show that the important influencing factor in the development of the arteriosclerosis in these 14 cases was poor control of the diabetes; as contrasted with previous methods of treatment, duration of the diabetes does not appear to have been an important factor. It will be noted that there were 28 individuals who had diabetes for more than five years and that 11 of these 28 were found to have cardiovascular disease when last examined. Though this incidence is very low compared with previous experiences with diabetes of the same duration, the probability is that it would have been still lower had these 11 people followed treatment carefully. It will be observed that compared with the 17 patients who did not develop cardiovascular disease, the average cholesterol was high and the control index was low.

SUMMARY

Combining all of the above experiences, it appears reasonable to conclude that excess blood cholesterol is an important etiological factor in the production of arteriosclerosis in the young diabetic. The data also appear to indicate that treatment with the high carbohydrate-low calorie diet has delayed development of cardiovascular disease in the cases investigated. Time alone and further studies will determine whether this diet can actually *prevent* premature development of this complication.

The findings in these 50 cases of diabetes are reported *in detail* for a definite reason. I believe I have clearly shown elsewhere that one of the most constant characteristics of the high carbohydrate-low calorie diet is an immediate and sustained decrease of plasma cholesterol. I believe this

finding is incontestable. Therefore, if the conclusion that excess cholesterol in the blood causes cardiovascular disease in the young diabetic is also found to be correct, the outlook of the diabetic has been greatly improved. Repetition of these studies is, therefore, warranted by others with similarly available facilities. In order, however, that other data may be comparable with our own, the method of investigation should be the same; the *combined* method of detecting arteriosclerosis should be used in *every* case. This includes, as previously stated, a *very careful* general physical examination; examination of the fundi; roentgen-ray examination of the lower extremities for calcification of the arteries and roentgen-ray examination (six foot plate) of the heart. As we have shown previously [2] any one method alone or any combination of two or three methods alone, does not afford a sufficiently reliable index of the presence, or absence, of arteriosclerosis. For the estimation of plasma cholesterol, *all blood samples should be collected in the fasting state;* and in the interpretation of cholesterol data, all conditions known to affect the concentration of cholesterol in the blood—that is, whether they increase or decrease it—other than diabetes and arteriosclerosis should be excluded as much as possible. In order that data of different clinics with respect to degree of control of diabetes may be reasonably comparable, it is also suggested that the control index reported here should be used. It appears to be a reasonably quantitative measure of control of diabetes from a statistical point of view. It is, at least, more reliable than use of such terms as good, fair, poor, etc. Finally, in interpreting blood cholesterol, differences noted should be judged by their *probable errors.*

I wish to take this opportunity of expressing my thanks to Dr. C. A. Peters, recently retired Chief of one of the Medical Services of this hospital; to Dr. A. H. Gordon and Dr. C. P. Howard, Chiefs of the Medical Services, who were, with very few exceptions only, responsible for all of the physical examinations; to Dr. S. H. McKee, Chief of the Department of Ophthalmology, who made all fundi examinations; to Dr. W. L. Ritchie, Director of the Department of Roentgenology, for the liberal use of his time in the interpretation of the roentgen-ray findings; to Dr. A. F. Fowler and Dr. E. H. Bensley for their assistance in the management of these cases in the wards; to Dr. Neil Feeney for his clinical examinations of the out-door cases to be reported upon later; to Misses Eleanor V. Bazin, Marjorie Mountford and Eileen Payette for the careful attention to details in the necessary collection and assortment of data; and to Dr. L. J. Rhea, our Pathologist, for his coöperation throughout this investigation.

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ELECTROCARDIOGRAPHIC STUDIES IN ACUTE CORONARY THROMBOSIS

I. TRANSIENT HEART BLOCK OF ALL GRADES IN A T_3, Q_3 TYPE OF CASE, WITH SERIAL ELECTROCARDIOGRAMS FROM ACTUAL ONSET TO AND AFTER CLINICAL RECOVERY *

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MUCH that is known concerning the electrocardiogram of acute coronary thrombosis has been deduced from the study of records made at various stages of the patient's illness and from short—often disappointingly short—serials. Smith's [1] animal experiments showed in a general way what might be expected. Herrick,[2, 3] Pardee,[4, 5, 6] Rothschild, Mann and Oppenheimer,[7] Levine,[8] and others, contributed importantly to the development of the present knowledge of electrocardiographic changes. Parkinson and Bedford [9] in 1928 contributed magnificently in their study of 28 cases. Their study not only summarized everything of importance that had previously been brought out, but they described in a more detailed manner than had previously been attempted transitions of the form of the ventricular complexes as they occur through the course of coronary occlusion, illustrating most of these mutations with electrocardiograms from their patients, and supplementing the information so given by the publication of a schematic illustration showing their concept of the general trend of such changes.

When Herrick, in 1919, published the first electrocardiogram from a case of acute coronary thrombosis the electrocardiograph was a stationary instrument, delicate, temperamental, and difficult of operation as those who have had experience with the instrument of those days will not fail to remember. At the onset and during the critical early stages of acute coronary occlusion conveyance of the patient to a place where an electrocardiogram could be recorded was interdicted by reason of the gravity of the patient's condition. Medical leaders such as Christian,[10] as recently as 1925 felt constrained to advise: " the obtaining of the electrocardiogram involves transportation of the patient; postpone it until the patient's condition has greatly improved, for rest is more important to the patient than an electrocardiogram. A live patient with a probable diagnosis of cardiac infarction is by far preferable to a dead one, definitely diagnosed by finding a typical electrocardiogram and the moving of the patient may make the difference between recovery and death."

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The evolution of the electrocardiograph to its present state of simplification of operation, reliability and adaptation to bedside use has made it practical without injury to the patient to study every phase of electrocardiographic mutation in acute coronary occlusion provided that we refrain from causing the patient to move except for the slight passive motion of the limbs incidental to application of the electrodes. Herrick [11] has called attention to the need of more detailed studies. No cogent reason remains why they should not be made in the three standard leads, and such studies should help immeasurably to clear up many muted questions concerning diagnosis, prognosis, localization and treatment. As to direct chest leads, although they have undoubtedly proved informative one is inclined to feel somewhat as Christian did in 1925. The application of electrodes for the chest leads involves moving the trunk of the patient. Only in selected cases without evidences of shock does this seem justified.

In view of the circumstances as outlined above it is to be considered a credit to the medical profession at large that no detailed serial electrocardiograms were made until the evolution of a new type of electrocardiograph made it practical to do so with safety to the patient. Thus Gilchrist and Ritchie [12] in April 1930, after making a survey of the literature noted the discrepancy between the immense volume of literature and the small number of cases reported in detail, remarking that "not until serial electrocardiograms became available was the electrocardiographic evidence of myocardial infarction placed on a satisfactory basis."

According to the writer's concept of what is possible with modern electrocardiographic apparatus there are less than a score of serial electrocardiograms in the literature which show sufficient detail—in at least a portion of the progress of average cases of acute coronary thrombosis—to permit of satisfactory analysis of the probable underlying pathology stage by stage. The T_1 case reported in 1929 by Moore and Campbell [13] remains the only case of acute coronary occlusion reported in detailed serial electrocardiograms from the date of actual onset to and beyond the date of clinical recovery, showing transition of the ventricular complexes as described by Parkinson and Bedford.

This is not to say that other good serials have not been published but rather, that in some instances, intervals between taking of graphs have been so long as to cause the omission of important mutations and changes of rhythm, and in others that so much time elapsed from the onset until the first electrocardiogram was recorded that all of the early transitions were missed. Such as they are, however, the serials now on record do show that a definite order of mutation of the ventricular complexes generally but not invariably occurs in the manner outlined by Parkinson and Bedford, and that most of the cases can be separated into one of the two classes described by them as T_1 and T_3 types. In a minority of cases the appearance of atypical or bizarre forms of ventricular complexes confuses the diagnostician; in others the complexes have the appearance of those seen in some stage of

coronary occlusion but, although the clinical picture is that of a case of recent acute coronary occlusion, there is failure on the part of the ventricular complexes to go through the typical stages of mutation of form.

The occasional failure of the electrocardiograph to record any diagnostic changes at the onset of acute coronary occlusion has been discussed by many writers. Wolferth,[14, 15] Wood,[16, 17] and co-workers have shown that in such cases (*a*) chest leads often clinch the diagnosis; (*b*) the greatest usefulness of chest leads is in T_1 cases since diagnostic changes usually occur in the standard leads in T_3 cases; (*c*) rarely both standard and direct chest leads fail to show diagnostic changes at the onset. It is to be observed in this connection that most of the cases reported in the literature purporting to show failure of the electrocardiogram to record diagnostic changes have been without the benefit of detailed serial electrocardiographic studies.

The case to be reported is one of a series of case studies in acute coronary thrombosis in which it was attempted to secure more detailed electrocardiographic serials than have previously been reported in a series of cases, the purpose being to add to the small number of satisfactory serials thus far published, thus increasing the material available for study and perhaps eventual solution of some of the problems previously referred to.

Case Report

WRGH., white male, aged 58. At 11:30 a.m. on December 7, 1932, he complained of symptoms of indigestion similar in character to attacks he had experienced off and on for 25 years. The heart sounds were clearly heard. The blood pressure was 158 millimeters of mercury systolic and 85 diastolic. He had no precordial pain at this time. The patient had led an active life. Polo playing was one of his favorite diversions. Except for "spells of indigestion with colicky abdominal pain" and a lifetime of constipation he had never been ill. His symptoms were relieved but returned late in the afternoon and hospitalization was advised.

Though he now felt well he consented to go to the hospital, laughing and joking in the automobile while en route, and was admitted at 6:10 p.m. At 6:55 p.m. he experienced the onset of extremely severe precordial pain, went into collapse and almost died. Heroic stimulation with caffeine sodiobenzoate and intravenous 50 per cent glucose revived him but he still looked exceedingly ill. The first electrocardiogram was made at the height of the attack while stimulants were being administered. A blood pressure reading could not be made at this time because of the pressing urgency of the emergency, but the patient was pulseless at the radial, brachial and femoral arteries, and heart sounds could barely be made out. The blood pressure, 30 minutes later, was 80 systolic and 50 diastolic. Other symptoms were blue-black cyanosis of the lips, dusky gray cyanosis of the skin, profound weakness, shock, profuse cold perspiration, restlessness and Cheyne-Stokes respiration.

Physical examination, after the acuteness of the attack had passed away, showed weak heart sounds, no murmurs, pulse feeble but regular at the right radial; no pulse at left radial (patient stated that this had always been absent). A few scattered moist râles were heard at the bases. Pain lasted 20 hours. It started over the precordium radiating to a point in the back between the scapulae. After the first few days the pain between the scapulae was more severe than the anterior pain, and as pain gradually subsided it was from this posterior point that it was last to disappear. During the first few days pain was also felt in both arms and forearms, and in the epigastrium.

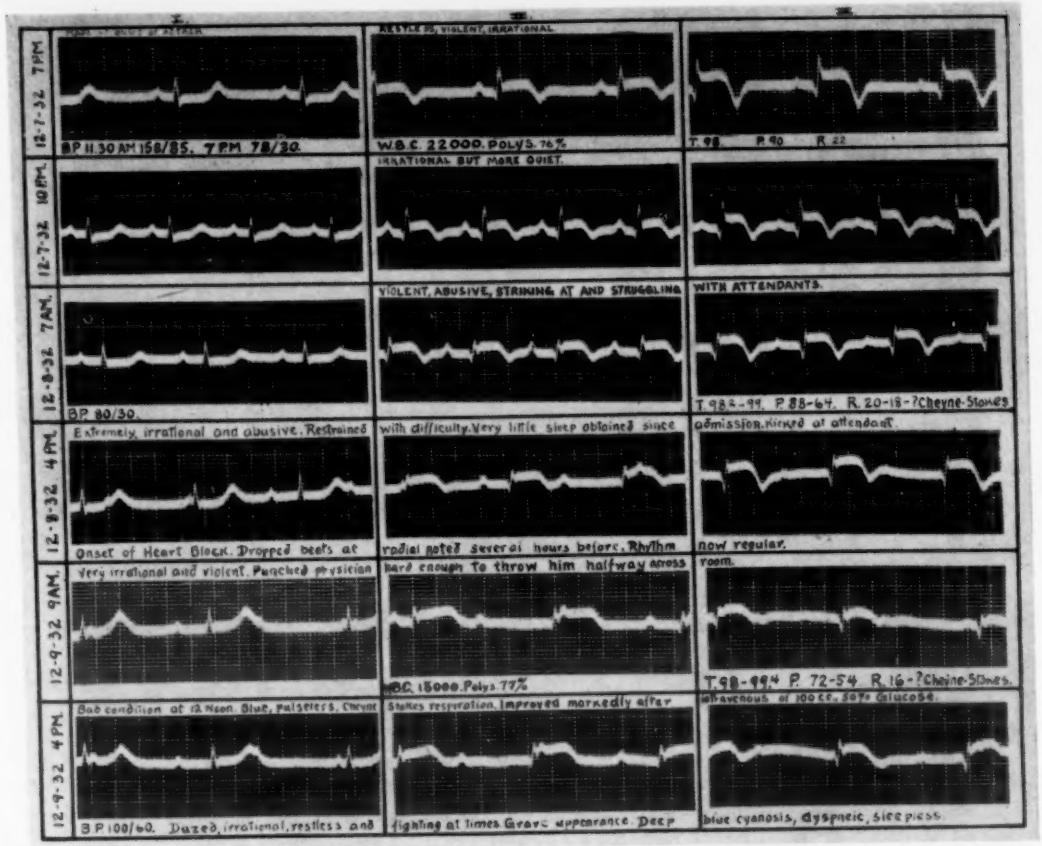

FIG. 1. Onset of acute coronary thrombosis to third day. (The electrocardiograms illustrated in this and in all of the succeeding plates were recorded without overshooting by means of a standard, mobile, string galvanometer. Deflections of 1cm-1mv. In the interest of conservation of space the graphs have been photographically reduced approximately 40 per cent.)

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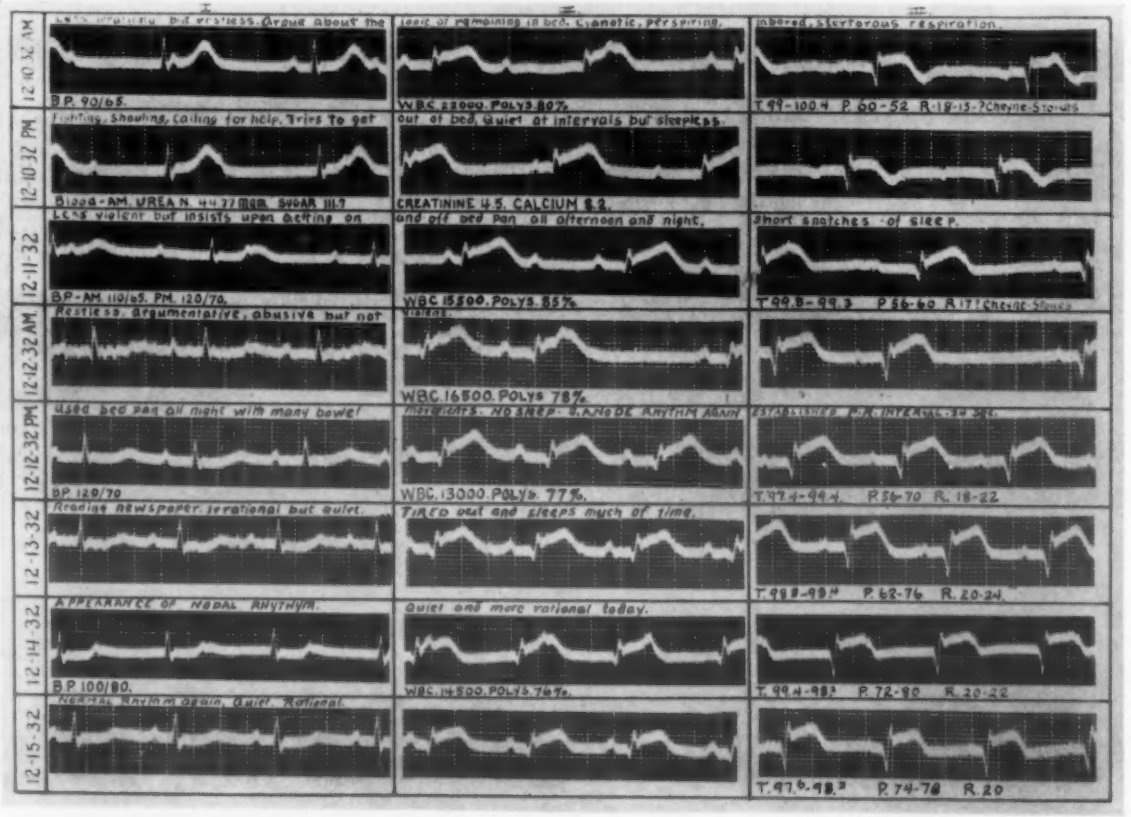

FIG. 2. Fourth to ninth days.

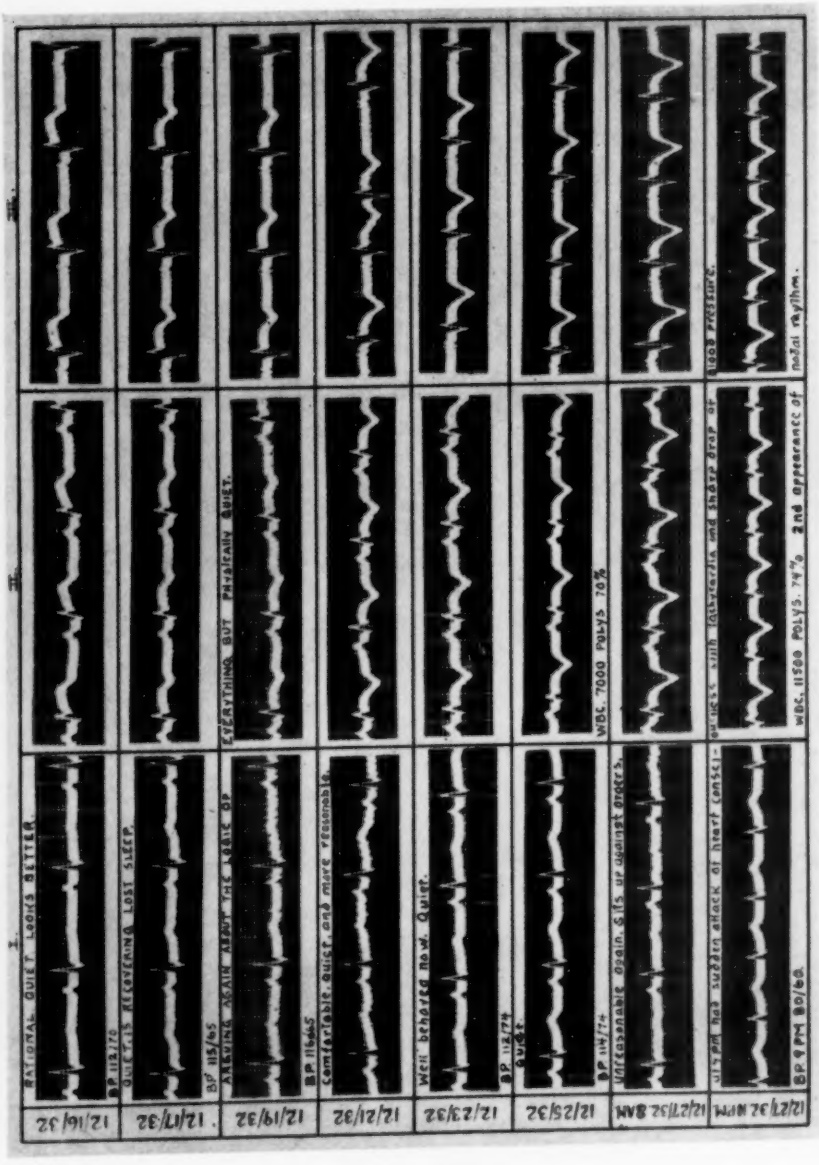

FIG. 3. Tenth to twenty-first days.

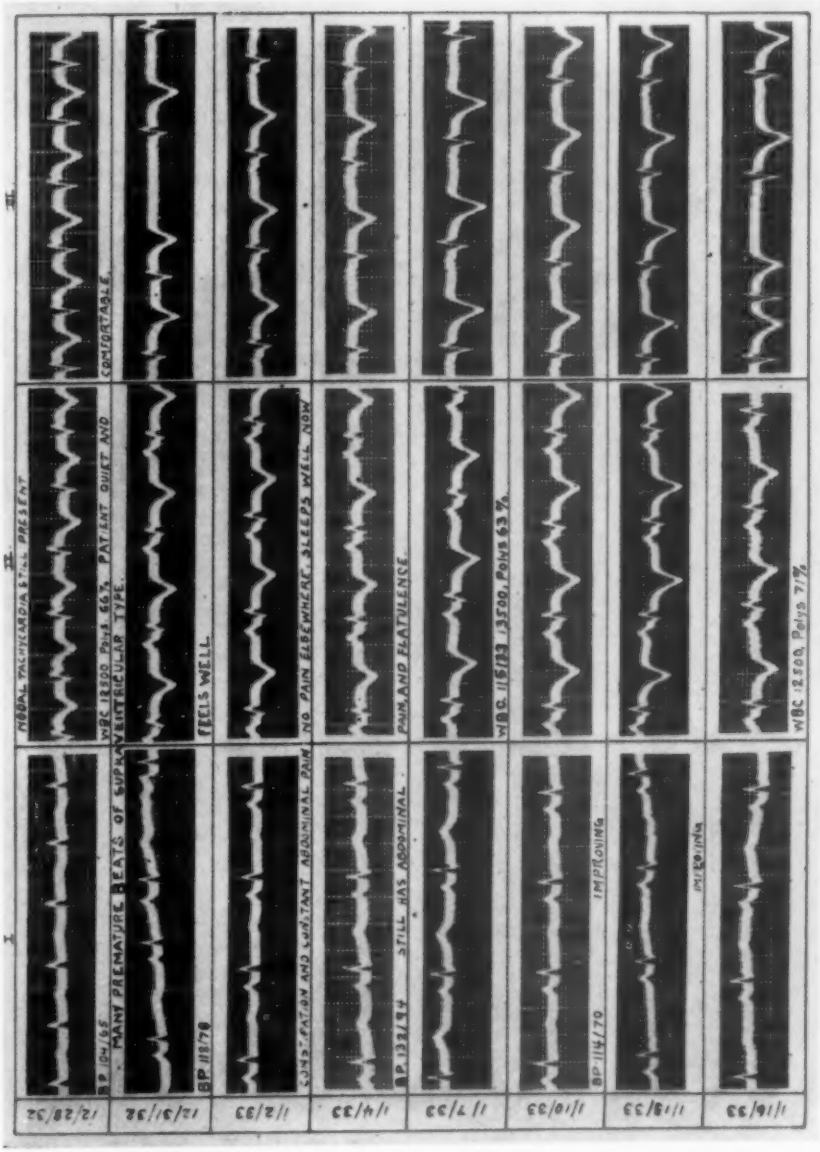

FIG. 4. Twenty-second to forty-first days.

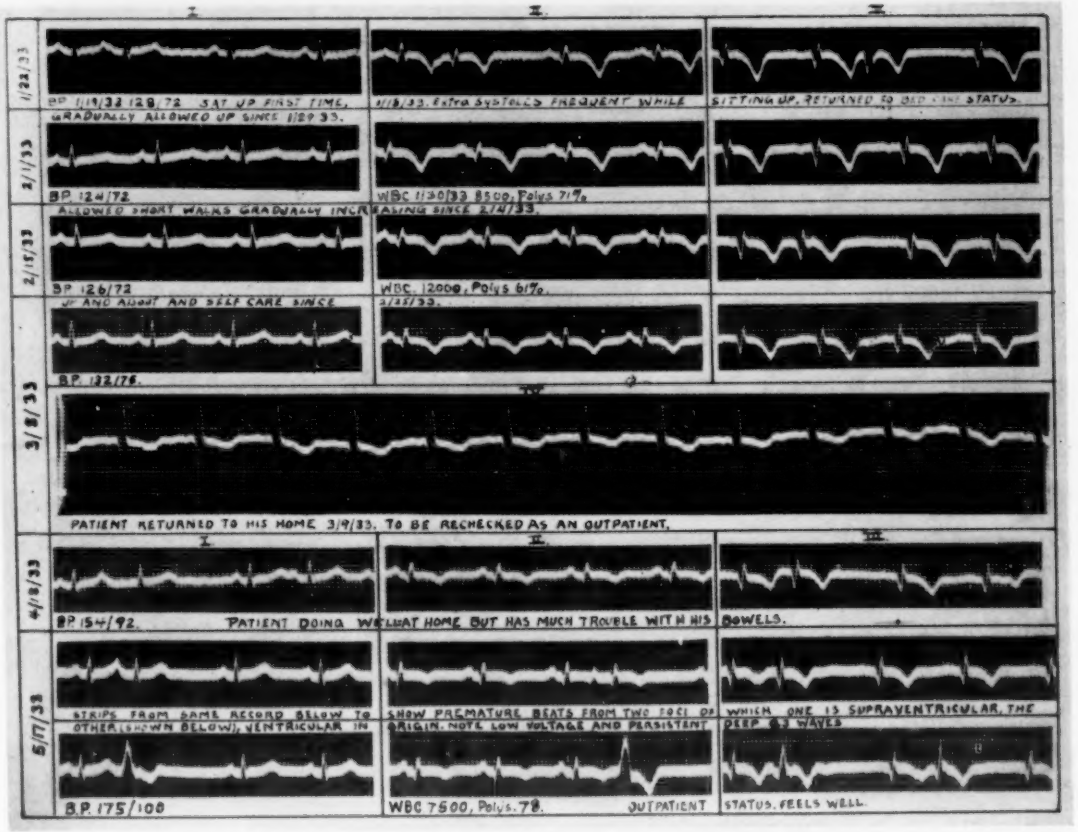

FIG. 5. Forty-seventh to one hundred sixty-second days.

Twelve graphs were recorded during this period. As electrocardiographic mutations are very slow during the stage of recovery, six of the records were omitted from this plate. In common with the graphs illustrated, they show how greatly the frequency of incidence of premature beats has increased during this stage. In this plate the record of 3–8–33 shows Lead IV in addition to the standard leads. This was recorded by means of direct chest leads according to the method of Wolferth and Wood. The patient is still living and active more than a year (June 1934) after the last electrocardio-

Blood pressure: A study of the blood pressure as recorded at annual physical examinations since 1918 showed that it had been within normal range until 1925. Thereafter there had been an annual rise, reaching 164 systolic and 100 diastolic in January 1930. From this time on the blood pressure was elevated. A few days before the onset it was 165 systolic and 85 diastolic. The effect of the thrombosis was a precipitous drop of blood pressure to nil as evidenced by the condition of the patient as described above. From the onset to March 1933 the blood pressure level was always distinctly less than it had been during a period of five years preceding the attack. After March the blood pressure gradually increased. Six months after the onset of coronary occlusion it registered 175 systolic and 100 diastolic. The systolic level at this point was greater than had ever been recorded in this patient over a period of 16 years.

Temperature: This was recorded every four hours during the febrile period. It was normal on admission, gradually ascending to reach a peak of 100.6° on the fifth day, then gradually and irregularly descending to return to the normal level on the twenty-third day.

Leukocytes: 22,000 at onset, dropping to 18,000 the third day, and returning to 22,000 on the fourth day during the second acute collapse. From the latter point the count gradually dropped, reaching 7500 the nineteenth day, then had a secondary ascent to between 11,500 and 13,000 until February, but was normal thereafter.

Course: No case hitherto reported in the literature has had a course as violent. Restless from the onset, the patient became tremendously violent again and again. This physical activity continued despite the constant day and night efforts of special nurses and attendants until the sixth day. During this period the patient was exceedingly abusive, restless and irritable. Whenever possible he kicked at attendants and on one occasion struck at an attending physician with enough force to throw him halfway across the room. At this time he did not seem to be sufficiently well oriented to identify individuals. Following this came a period of two weeks during which the patient insisted upon getting up and about, attempting to accomplish by argument and "logic" what he had formerly attempted by violence. The last unreasonable spell occurred on the twenty-first day when he sat up in bed against orders, and threatened to get out of bed. The results were sufficient to quell the last notions of physical resistance which the patient entertained, as a nodal tachycardia promptly ensued and lasted for 24 hours causing him to feel as "weak as a kitten." During January he had the most extraordinary amount of intestinal flatulence, with the constant desire to relieve it by means of enemas. There were days when he seemed to be on the bed pan nearly all the time, with inadequate results. This trouble gradually lessened but, even when able, later on, to be up and about, and since leaving the hospital, constipation and intestinal flatulence have been a difficult problem for him.

Electrocardiograms: The first graph of December 7, 1932, taken at the onset of the attack, shows depression of the R–T segment in Lead I with elevation of R–T segments in Leads II and III. Take-off of T is direct from the descending limbs of R-waves in Leads II and III. T-waves have an upward convexity above the base line in Leads II and III followed by a downward projection of about equal amplitude extending as a pointed tip below the isoelectric level. Q_3 is well developed and of the type which Pardee[18] considers significant. Another graph the same day and two the following day showed much the same characteristics except that reduction of amplitude of QRS developed rapidly. After this there was a period of eight days during which the T-waves of Leads II and III became sharply convex, upright waves with take-off ascending the R-wave, losing their negative projections. At the same time T_1 became altered. It became greater in height and breadth until the fourth day. Then it lost amplitude rapidly and the Q-waves in Leads II and III became especially well developed. In the latter lead they were at times the tallest deflections of QRS to be found in any lead. On the tenth day small negative projections of T again ap-

ard leads. This was recorded by means of direct chest leads according to the method of Wolferth and Wood. The patient is still living and active more than a year (June 1934) after the last electrocardio-

peared in Leads II and III. From that date forward the T-waves in these two leads gradually increased in depth below the isoelectric level until, on the thirty-second day their point of maximum inversion was reached. After that they gradually diminished in depth from graph to graph. The amplitude of QRS never returned to anything approaching that found in the first record, and the deep Q_3 waves, still of the significant type appear to have become a permanent fixture.

Rhythm: The P–R interval in the two graphs of the day of onset was .16 second. By the next morning it measured .23 second, and that afternoon complete heart block was established. At this time the rhythm was absolutely regular; but several hours before, second degree heart block with dropped beats * had been noted by clinical observation. Complete heart block was present without intermission during the third, fourth and fifth days. Although the ventricles were rhythmic and slow, the rate of the auricles during this period was, for a time, nearly as slow and there was noted a rhythmic waxing and waning of the amplitude of the P-waves. Only sections showing sizeable P-waves were included in the serial shown in the plates in order that the daily progress of the abnormal rhythm might better be visualized. Hundreds of feet of electrocardiogram were recorded during the three days when complete heart block was present. Much of this record showed a waxing and waning of amplitude of the P-waves as described, but there was no irregularity of rhythm of the ventricle, no relation between incidence of auricular and ventricular waves, and no wandering of the auricular pacemaker.

On the morning of the sixth day second and first degree heart block were present, the former predominating. The section in the serial from Lead I was inserted to show an interval of prolongation of A–V conduction time only while sections from Leads II and III were cut to show the predominant second degree heart block. Normal sinus rhythm was more permanently established the same afternoon but with prolonged conduction time. This lasted only 24 hours when nodal rhythm with slow retrograde conduction to the auricles appeared. The next day sinus node rhythm was reëstablished, with normal P–R interval. This continued until the afternoon of the twenty-first day when nodal tachycardia suddenly appeared after the patient sat up in bed against orders. This persisted about 24 hours. It was terminated by the use of quinidine. Following this, sinus node rhythm prevailed but premature beats were frequent. In the last graph made on the one hundred sixty-second day many premature beats from supraventricular and ventricular foci were recorded.

Comment

The principal clinical happenings have been noted on the plates illustrating the serial electrocardiograms and for sake of further convenience have been summarized in table 1. If the reader will follow them it will be observed that close clinical-electrocardiographic correlations can be studied from the actual onset and mutations of the graphs from stage to stage are so gradual that it is possible to compare these changes with the schematic concept of what such transitions should be as formulated by Parkinson and Bedford.

At the onset marked elevation of the R–T segments is recorded in Leads II and III and opposing such elevations there is slight but definite S–T depression in Lead I. According to the schematic concept R–T, S–T take-off

* Further examination of the long record of that morning revealed the presence of a single dropped beat due to momentary second degree heart block. Throughout the remainder of the graph first degree heart block with P–R interval constant at .23 second is recorded.

TABLE I

Day	Rhythm	Ventricular Complexes in Lead III	Clinical Correlations
1	Of S-A node origin. No heart block. No premature beats.	T diphasic. R-T take-off high; halfway up R-waves. QRS amplitude less than normal, but greater than later on.	Some struggling but quiet as compared with succeeding days.
2	First, second, third degree heart block in succession.	T diphasic. Amplitude of QRS diminishing. Take-off of R-T from higher point of R-waves.	Struggling constantly. Extremely violent. Maximum drop of blood pressure.
3, 4, 5	Complete heart block, A-V ratio varying from 86 : 53, third day to 102 : 47, fifth day.	T diphasic, changing on fifth day to monophasic. QRS low amplitude. R-T take-off maintained at higher level.	Perpetual struggling, day and night.
6	Second, then first degree heart block.	T decidedly monophasic. QRS amplitude diminishing. R-T take-off higher.	Less struggling. Mostly quiet. Worn out.
7	S-A node rhythm. No heart block.	Same but very high arched T-waves.	Sleeping.
8	Nodal rhythm: onset S-A block, 2 cycles, followed by ventricular escape.	Height of R-T take-off above base line diminishing.	Quiet most of time.
9	S-A node rhythm.	Same. Q_3 very deep.	Quiet.
10	S-A node rhythm.	T slightly diphasic. R-T elevation diminishing.	Quiet. Temperature peak next day.
15	S-A rhythm	R-T level isoelectric. T_3 all inverted.	Quiet.
21	S-A rhythm changing in p.m. to nodal tachycardia.	T less deeply inverted with tachycardia in p.m.	Unreasonably sitting up. Momentary BP drop.
22	Nodal tachycardia.	No change.	Quiet.
25	S-A node rhythm with nodal premature beats.	QRS amplitude very low.	Quiet.
32	S-A rhythm.	Point of maximum inversion of T_3.	Quiet.
163	S-A node rhythm with nodal and ventricular premature beats.	Very low amplitude QRS. Permanent deep Q_3. T_2 and T_3 still inverted.	2 mos. out of hospital. No cardiac symptoms. Unwisely overactive.

should gradually approach the isoelectric thereafter; but the reverse is true here. The two graphs made on the day of onset show the R–T take-off about half-way up on the descending limb of R_3. The level of take-off is higher next day, and on the succeeding four days becomes still more elevated. It is not until the eighth day that the opposite trend is manifested. Thereafter gradual descent is illustrated, the isoelectric level being reached on the fifteenth day.

Transitions of the form of the T-waves also occur at first in reverse order. At the onset, in Leads II and III the T-waves have positive followed by negative deflections of about equal degree while the low take-off of T_1 gives it a somewhat stilted upright appearance. From this point onward the negative tip of the T_3 wave becomes less and less conspicuous until, by the fifth day, it is gone and we see what Parkinson and Bedford described as a " monophasic " curve of the ventricular complexes. Following still further the upward bowing of this curve, or the amplitude of T_3 if we so prefer to refer to it, becomes more and more sharply marked reaching a peak of amplitude on the seventh day. From this point onward the course of electrocardiographic events definitely follows the schematic concept of Parkinson and Bedford. The suggestion of a negative projection of T_3 again occurs on the tenth day, it is definite on the eleventh day; then on the fifteenth day *all* of T_3 is negatively directed. From graph to graph after this we notice the T_3 wave becoming gradually more deeply inverted. A turning point, the point of maximum inversion of the T-wave in this lead is arrived at by the thirty-second day. Succeeding records show the degree of negativity receding just as gradually. The T-waves of Lead II throughout followed much the same course as did those of Lead III.

In Lead I after the onset the T-waves became more and more prominent for a time. When their amplitude peak was reached on the fourth day they were large, broad and conspicuous waves with a stilted appearance. After this their amplitude diminished rapidly. On the twenty-first day and again on the thirty-eighth day they were so low as to be practically isoelectric. Latterly they again gradually increased in size. By the sixth month they were once more of fair amplitude and still positive.

The Q_3 wave was significantly deep at the onset. It gradually gained amplitude until, on the eleventh day it was the tallest of any of the deflections of QRS in any lead. Thereafter it gradually declined in size, but even in the last graph remained significantly deep. Q_2 waves were also quite well developed except at the onset. Diminution of voltage of the QRS complexes also affected the amplitude of Q_3 waves, but their relative size from graph to graph seemed to vary in direct proportion with the amplitude of R_1.

As to alteration of the QRS complexes, their amplitude was quite low at the onset, but voltage dropped still further from graph to graph. After six months, at which time the patient was entirely free of cardiac symptoms and actively going about his business, the amplitude of QRS remained as low, perhaps, as it had been at any time.

Clinical-Electrocardiographic Correlations

How can this seemingly complex series of EKG events be correlated with the probable happenings within the heart of this patient? Why does this series of changes of the R–T levels and of the mutations of QRST com-

plexes seemingly fail to follow the schematic concept of Parkinson and Bedford? Why does the take-off of the R–T serially ascend the R-waves before it changes course to descend and finally reach the isoelectric level? Why do the T-waves change from diphasic to monophasic waves before again changing to the diphasic and then to the completely inverted form? These are some of the questions which occasional electrocardiograms taken haphazard at a few of these phases of transition cannot answer. Their solution can only be attempted on the basis of a serial composed of frequently repeated graphs with clinical detail in sufficient wealth to permit of the formulation of a fairly complete estimate of probable cause and effect.

The probable course of events within the heart of this patient seems quite clear. Thrombosis at the onset probably affected only the terminal portions of the right coronary artery. A–V conduction was not impaired because the blood supply to that node was not inadequate. Beginning on the second day and terminating on the sixth day the violent physical struggles of the patient were almost incessant. This was the cause of the next event—heart block. It was probably brought about as a result of gradual shutting off of the direct blood supply when ascending thrombosis passed the point where the artery supplying the A–V node branches off from the posterior portion of the right coronary artery. This resulted in the appearance in the EKG of first degree heart block. At this point the collateral blood supply to the A–V node derived from the left coronary artery was in all probability quite good. The appearance in turn of a second degree and complete heart block might never have happened were it not for the fact that the violent struggling of the patient brought him to a state of relative insufficiency of the collateral supply. Thus heart block, in all of its phases, was only transitory. As the patient became less violent the collateral blood supply became relatively less and less inadequate. The EKG evidence of this is reversal from complete to second degree block; then from second to first degree block. On the seventh day when the patient, finally completely exhausted as a result of his heavy labors, slept throughout most of the day, all traces of A–V block disappeared—the collateral supply to the A–V node was adequate.

Did the ascending thrombosis go further? If it came around anteriorly almost to the origin of the right coronary artery it would shut off the branch usually supplying the S–A node. This would result in wandering of the pacemaker or sino-auricular block. This did not occur, but the peculiar waxing and waning of the amplitude of the P-waves would seem to suggest that the supply to the pacemaker also, was inadequate. This waxing and waning of amplitude was present only during the period of heart block. The physical exertion of the patient here again probably resulted in relative insufficiency of the blood supply to that node, as the auricular waves promptly became normal after he became quiet. It is not improbable that narrowing of the lumen of the blood vessel supplying the node was already present. Otherwise a state of relative inadequacy of circulation would not have been so readily produced by exertion. The transitory nodal rhythm

and nodal tachycardia that appeared later on were most likely due to the same cause.

After the sixth day the patient became quiet and remained so. If we will study the course of the EKG with the viewpoint of a person who has made the first EKG at that point, it will at once be seen that all of those changes which Parkinson and Bedford referred to as a monophasic curve are present. There is perfect R–T fusion. The take-off of T is very high on the descending limb of R in Lead III. There is no suggestion of a downward tip of T_3 pointing below the base line. Following further all of the mutations described by Parkinson and Bedford are in turn manifested until the R–T take-off reaches the isoelectric level, R–T fusion disappears and T is *all* inverted. During this period it is probable that no further ascending thrombosis occurred. Collateral circulation due to the quiet of the patient was adequate for the low level of physical activity present. It was sufficient during the stages of organization of the thrombus and infarct to keep the nodes supplied, to permit of normal conduction through the unaffected portions of the heart, and of eventual clinical recovery of the patient. The reminders that permanent damage had been accomplished were the electrocardiographic residuals—extreme low voltage, deep Q_3 and inversion of T-waves in Leads II and III.

The explanation of the probable course of events within the heart as given above would have seemed fanciful and improbable only a few years ago. At this date there is more than the clinical-electrocardiographic comparison, event by event, to cause this line of reasoning to be more certain than hypothetical. Further on in this paper the background of facts supporting it will be stated.

There is every reason to believe that a quiet patient runs less risk of death from coronary thrombosis than otherwise. The dangers of an ascending thrombosis are feared by every clinician. No matter how they may disagree about whether to give digitalis, glucose, theophylline, caffeine and other drugs, practically all authorities agree that morphine must be given, and in doses large enough to secure relief from pain and quiet on the part of the patient. To this patient morphine was given, and in large enough doses to have caused an average coronary patient to go into coma. But morphine had an antagonistic effect in this case. Instead of promoting quiet and relieving pain, each injection was followed by increased pain and physical activity. When quiet was finally secured it was through the use of sodium amytal. After that the patient went on to an uneventful clinical recovery. The liberal use of injections of caffeine sodio-benzoate and intravenous glucose undoubtedly saved his life during the early days of the thrombosis. Because of potential dangers from the use of the latter it was not given until the patient looked as though he most surely would die. At this point he was cold, pulseless, weak, with deep blue black cyanosis of the lips, dusky gray, almost leaden color of the skin, drenched with perspiration, restless, and with Cheyne-Stokes respiration with long apneic phases.

Notwithstanding the grave condition pictured, the response to glucose was astonishingly prompt. The pain and restlessness were intensified as the patient came back to life, but the shock, cyanosis, and abnormal respiration disappeared; the pulse became palpable, the heart sounds of better quality; the blood pressure increased and he no longer presented the same preagonal appearance. Sodium amytal has been said to lower the blood pressure [37] and the use of intravenous glucose in 50 per cent concentration is a dangerous procedure.[38] It is not our intention here to advocate their use except in carefully selected cases, but rather, by stating how and why they were used in this case, to furnish further material for comparison with the clinical and electrocardiographic events. It may be observed, however, that in a similar T_3, Q_3 case with complete heart block and Cheyne-Stokes respiration, Bell and Pardee [19] were able to save the life of their patient with the aid of intravenous 50 per cent glucose, and felt that "dextrose intravenously merits trial." Their case also had a stormy course. Other cases of like nature with great restlessness have died.

Discussion

Parkinson and Bedford in 1928 divided their cases of coronary occlusion into T_1 and T_3 groups. They suggested that "the particular coronary branch occluded would determine the lead in which T inversion would occur" and that the T_1 and T_3 types of curve "represent occlusion of different branches." This seemed all the more probable to them in that their case 1 had two separate attacks of coronary thrombosis during a period of two years. The "first attack was followed by the T_1 type of curve and the second by the T_3 type."

Following this up, Barnes and Whitten [20] in 1929, after extensive clinical, electrocardiographic and necropsy studies concluded that "an electrocardiogram of the T_1 type is associated with infarction of the anterior portion of the left ventricle supplied by the average left coronary artery" and that "an electrocardiogram of type T_3 was found to be associated with infarction in the posterior portion of the left ventricle in the region usually supplied by the right coronary artery."

Electrocardiograms made in cases of wounds of the human heart,[21, 22, 23, 24] experimental studies on animals,[25, 26] and clinical and necropsy findings of other observers [27] have confirmed the opinion of Barnes and Whitten insofar as pertains to the electrocardiogram of the average human heart. There are some exceptions of course, but it is probable that they are no more frequent than is variation in the distribution of main coronary branches in exceptional hearts.

Wood and co-workers noted in particular, among other of the principal findings in T_3 cases the presence of a deep Q_3 wave. It is well illustrated in all of their published electrocardiograms of the T_3 type. It should be

observed that Q_2 also was very conspicuous in all of their T_3 electrocardiograms. In a study of electrocardiograms from cases personally observed and from the literature in cases electrocardiographically studied soon after the onset the writer found that either at the onset or some time during the course in T_3 cases: (*a*) both T_2 and T_3 were inverted; (*b*) 85 per cent had significantly deep Q_3 waves; 63 per cent had well developed Q_2 waves in addition to having significant Q_3 waves. In the absence of R–T, S–T segment deviations the finding of these four changes seems to afford more definite evidence of acute or recent coronary occlusion than does the finding of either of these changes singly.

In the case here reported elevation of the R–T intervals in Leads II and III, inversion of T_2 and T_3 waves, deep Q_2 and significant Q_3 waves are findings all of which are classical and typical of thrombosis of the right coronary artery.

In order to understand the probable effect of ascending thrombosis in the right coronary artery it is necessary to emphasize certain observations concerning the average distribution of that artery. When cardiac infarction occurs as a result of occlusion of the right coronary artery, as pointed out by Parkinson and Bedford and Barnes and Whitten, infarction seldom involves the muscle of the right heart. Even in Barnes and Whitten's Case 12 in which "The right coronary orifice was plugged by a thrombus, all of the right ventricle except a small area adjacent to the septum escaped infarction."

The T_3 type of electrocardiogram is believed by these workers to indicate infarction of the posterior portion of the left ventricle, or more specifically, only that portion of the left ventricle supplied by the terminal divisions of the right coronary artery. The inference is plain that, although the actual infarct is so limited, the occlusion within the right coronary artery may extend even to its orifice. Unless coronary sclerosis is unusually extensive within the vessels supplying the collateral circulation to the right heart it is probable that there is nearly always enough collateral blood supply to nourish it even though its main artery is completely occluded.

Although Barnes and Whitten did not find much evidence of infarction of the right heart in their cases, such infarction has been reported by others, and even aneurysm of the right ventricle has been reported; but such case reports are rare. In the case here reported, and for the reasons given below, it is believed that there was infarction of a portion of the right ventricle.

According to Gross,[28] in the average heart the fourth from last main posterior descending branch of the right coronary artery is the *ramus descendens posterior*. In 92 per cent of human hearts he found this vessel giving off the *ramus septi fibrosi* which supplies the A–V node. It was especially noted by him that the *ramus septi fibrosi* receives anastomoses

from the superior septal branches of the left coronary artery. He pointed out that by this means there is available a collateral supply for the A–V node whenever the main source—the *ramus septi fibrosi*—is blocked.

Haas [29] cited a case in which such anatomical construction was borne out in a heart where the *ramus septi fibrosi* was blocked by embolism. Hemorrhagic infarction of the muscular divisions which enter into the nodal structure occurred but the *anterior portion of the node was preserved* though much altered by inflammation. Haas explained this preservation of a portion of the node on the basis of collateral supply received from anastomoses with branches of the left coronary artery.

Kugel,[30, 31, 32] studied 50 normal human hearts and found in all of them a large vessel which he named the *arteria anastomotica auricularis magna,* a branch of the left coronary artery. In 66 per cent of hearts he found that it anastomosed freely with the artery supplying the A–V node. In the remainder he found two main variations, but in each of these the artery was so situated that its anastomoses with the right coronary artery were anterior, and far more proximal to the orifice of that vessel than is the point of branching off of the *ramus descendens posterior.*

Whether from the *arteria anastomotica auricularis magna* of Kugel or from the anastomoses of the *ramus septi fibrosi* with the superior septal branches of the left coronary artery of Gross, it is obvious that the A–V node generally has available a rich collateral blood supply whenever its usual source derived from the right coronary is shut off.

It is probable that only rarely does that node fail to receive a proper blood supply. Acute thrombosis of the right coronary plus extreme sclerotic narrowing of the opposite coronary or of its branches could do this. Occlusion of the right coronary, sclerotic narrowing of the left coronary and temporary insufficiency of blood supply through the left coronary by reason of congestive heart failure or extreme physical exertion could accomplish the same result. In the case here reported it is the most satisfactory explanation of the transient heart block. In a heart already seriously crippled by right coronary thrombosis as here obtained there can be but little doubt that whatever collateral supply was being received through anastomotic branches from a probably sclerosed left coronary artery must surely have been rendered insufficient due to the tremendous struggles of the patient.

As to the sino-auricular node, it is supplied by the *ramus ostii cavus superioris,* a vessel that Gross says " is not absolutely fixed in its origin, for it may arise from either right (60 per cent) or left (40 per cent) coronary artery " and furthermore " there are never two *rami ostii superiores,* always only one."

As before pointed out, occlusion of this vessel might cause wandering of the pacemaker or sino-auricular block. In the case here reported it is probable that the occlusion of the right coronary artery did not extend far enough

anteriorly to occlude the *ramus ostii cavus superioris.* The waxing and waning of amplitude of the P-waves, as noted was more likely due to relative insufficiency of the coronary circulation as a whole due to violent over exertion of the patient. There may also have been present some degree of sclerosis of the proximal artery or of the *ramus ostii cavus superioris.*

The late development of a high take-off of R–T segments has been noted previously by Levine and others. In Levine's case 56 a high take-off developed nearly two months after the onset, but unfortunately no graphs were obtained during the first month after the onset. Thus there was no means of comparing the electrocardiographic status at the two periods. In his case 61 the graph made at the onset does not show a high R–T take-off, but on the second day elevation in Leads I and II is plain, and by the fourth day is marked. Here again the graphs after the fourth day were not made often enough to follow the subsequent course of events, as only three more electrocardiograms were made in the subsequent 26 months. In the case here reported the serial graphs are the first to show both gradual ascent and gradual descent of the R–T segments.

Ball,[33] in a serial of 14 electrocardiograms, was the first to publish a satisfactory serial study of coronary thrombosis with temporary complete heart block. His explanation of the transient nature of A–V dissociation during an attack of coronary thrombosis on the basis of the peculiar anatomy of the blood supply to the A–V node is, with minor exceptions, concurred in by the writer and has been used in part to explain the development of heart block in the case here reported.

The present case study is the twentieth of coronary thrombosis with complete heart block reported in the literature. Ball listed 16 cases derived from the literature and personal communications, overlooking the two cases reported by Wearn [34] in 1923. The nineteenth case has been published more recently by Wood and co-workers.[35] Of the 20 cases, electrocardiograms were made in 18. There were 16 T_3 cases and two T_1 cases. In Sanders'[36] case, necropsy showed thrombosis of the right coronary artery with infarction of the greater portion of the outer wall of the right ventricle extending to the apex and to the anterior and posterior portions of the interventricular septum. His case illustrates quite well how even the right ventricle and septum may be extensively involved by infarction in thrombosis of the right coronary artery, though as previously stated, this is exceptional.

Summary

A case of acute coronary thrombosis is reported which is one of exceptional interest for the following reasons:

1. It is the first case to be reported with serial electrocardiograms at close intervals covering every form of transition of the ventricular complexes from the actual onset of acute coronary occlusion to and beyond the point of clinical recovery. The serial consists of 36 graphs.

2. The gradual mutations of the ventricular complexes can be compared stage by stage with the schematic concept elaborated in 1928 by Parkinson and Bedford. Close clinical-electrocardiographic comparisons are so facilitated by the detail shown in the serial graphs as to enable one to form a reasonable idea of the changes actually taking place within the heart from one phase to another, and to explain how and why they differ in some stages from the succession of changes predicted by Parkinson and Bedford.

3. The case is the twentieth of acute coronary thrombosis with the complication of complete heart block to be reported in the literature.

4. The electrocardiographic changes accompanying probable ascending thrombosis of a coronary artery are serially depicted and correlated with clinical observations.

5. Features of the electrocardiogram tending to make the presence of a significantly deep Q_3 wave, in certain instances, more diagnostic of coronary thrombosis are discussed and illustrated by the present case.

Since the preparation of this paper for publication the patient suffered a severe injury resulting in death August 31, 1934. Necropsy, unfortunately, could not be obtained. Prior to sustaining this trauma he had been active physically, with fair tolerance to effort and no complaints referable to his heart. Coronary disease had no connection with his death, nor with the injury responsible for death. Electrocardiograms supplementing those illustrated in this paper were recorded February 28, 1934, March 10, 1934, and August 3, 1934. The first two were essentially the same as the illustrated graph of May 17, 1933. The last EKG, recorded 28 days before death (20 months after the onset of acute coronary thrombosis), showed some changes. QRS had increased noticeably in width and amplitude. R_2 and R_3 were badly slurred. The tallest deflection of any lead (R_1) measured 5 mm. Q_2 and Q_3 measured 1.5 mm. and 3 mm. respectively. T_2 was very broad and flat, but was slightly positive.

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THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM"; A REVIEW OF RECENT AMERICAN AND ENGLISH LITERATURE ON "RHEUMATISM" AND ARTHRITIS *

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IN THREE PARTS

PART II †

CONTENTS: PART II

CHRONIC ARTHRITIS

WHEN one uses this term, one is generally speaking of either chronic atrophic or chronic hypertrophic arthritis, the two great forms of "chronic arthritis" which Osgood [187] calls the most generally prevalent and most inadequately treated controllable chronic disease. It is important to use a more specific term than just chronic arthritis and to distinguish between the two forms, as they are probably of quite different etiology; their symptoms and many of their physiologic aberrations are different, their treatment is by no means identical, and above all their prognosis is quite different. These differences have been fully reviewed in the *American Committee's Primer on Rheumatic Diseases and Chronic Arthritis,*[188] to which the reader is referred.‡ The essential differences are briefly these: Chronic atrophic

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† Part I appeared in the ANN. INT. MED., 1935, viii, 1315–1374.
‡ The "Primer" and "Exhibit" can be purchased from the American Medical Association, Chicago, for thirty cents. A statement of British National Medical opinion on chronic arthritis is also available (see reference 383).

(infectious, proliferative, rheumatoid) arthritis may appear at any age but generally does so between the ages of 20 and 40. It involves many joints, small as well as large. If of consequence, it is generally associated with loss of weight and appetite, secondary anemia, atrophy of skin, muscles, and bones, lowered blood pressure and skin temperature, and with other symptoms of vasomotor instability, exhaustion and tachycardia even without fever. Its course may be short and leave little or no significant residual disability. On the other hand it often tends to be progressively destructive, and in uncontrolled cases may end in ankylosis. Its pathologic characteristics in peripheral tissues are fibrous thickening and subcutaneous nodes, and in bone decalcification and infiltration of the epiphysis by nests of small round cells; in articular structures there are synovial proliferation and pannus formation, destruction of cartilage, marginal lipping of bones, and fibrous or bony ankylosis.

Chronic hypertrophic (senescent, degenerative, osteo-) arthritis, on the other hand, rarely appears symptomatically before the age of 40. It tends to involve a few favorite joints, such as the lower cervical and lower lumbar spine, terminal and sometimes middle (rather than the mid- and proximal) phalangeal joints, knees, and less frequently a hip or a shoulder (in the latter situation generally a bursa). Its course may demonstrate little progression; if so, the progression is slow and the disability it produces fairly moderate. It is not associated with a related loss of appetite and weight, anemia, tachycardia, hypotension, or marked alterations in skin temperature, although it is usually associated with some fatigue. Its pathologic characteristics in peripheral tissue are generally none except perhaps minor periarticular thickening; in bone there is no atrophy; in articular structures there are minor synovial fibrosis without pannus formation, cartilage degeneration and sometimes disappearance, early proliferation of marginal and subchondral epiphyseal bone, and no ankylosis except to some degree in the spine as bony spurs may coalesce.

Nomenclature. Just as with religion, politics, or prohibition, the subject of the nomenclature and classification of the chronic arthritides arouses vociferous, even acrimonious, debate. No classification of these two joint diseases is satisfactory for all purposes. For various reasons, chiefly to avoid the impression that knowledge on etiology is complete, the American Committee for the Control of Rheumatism has approved the terms " atrophic " and " hypertrophic " arthritis even though as individuals some of the committee members may be in the habit of using other designations. With permissible didacticism one may on occasion wish to use clinical designations (infectious arthritis, senescent arthritis) based on presumed etiology. Under other circumstances one may prefer to use a pathologic terminology: proliferative arthritis, degenerative arthritis. Still again a nomenclature in radiologic terms may be preferable.

An etiologic classification based on complete proof may, it is hoped, eventually replace all others. In the meantime the others are but working

classifications. As long as one realizes the limitations of each term, understanding, for example, that "proliferative arthritis" implies proliferation of synovia not of bone and is therefore the clinical opposite and not the clinical or pathologic equivalent of "hypertrophic" arthritis (which implies proliferation of bone, not synovia), as long as one does not entertain the notion that infection as the cause of "infectious arthritis" is proved with finality, or that all arthritis that shows hypertrophic changes in roentgenograms is "hypertrophic arthritis" in the sense of being the clinical equivalent of senescent arthritis, one should be at liberty to use whatever term seems most appropriate at the moment. He who wishes to be completely noncommital will probably favor the English designation: rheumatoid arthritis and osteo-arthritis. In place of "rheumatoid" or "atrophic" arthritis, the term "infective" arthritis is preferred by Miller [133] who believes it is due to streptococcal infection. With similar leanings the term "infectious arthritis" is approved for general use by Cecil (1929), Hench (1930), Kauffman,[189] Buie,[190] and many others. The term atrophic arthritis is favored by Pemberton,[191] Osgood,[187] Matz,[192] Holbrook,[193] Eaton,[194] Rich,[195] and others. Shapiro [196] comments on deficiencies of all classifications and (as did A. G. T. Fischer, 1929) suggests for each form a combined term indicating the clinical, etiologic (wherever possible), pathologic, anatomic, and roentgenologic characteristics of the disease at any particular moment. Thus he would speak of subacute, gonorrheal, proliferative monarthritis, of "hypertrophic arthritis" as chronic degenerative, chondro-osseous, hypertrophic polyarthritis, of "atrophic arthritis" as chronic, streptococcal, proliferative (periarticular atrophic) arthritis. For hypertrophic (senescent) arthritis, Miller [133] and others favor the term suggested by von Müller, "osteo-arthrosis," rather than osteo-arthritis, as the disease is degenerative rather than inflammatory.

In congress, physicians should use a common parlance, and in this paper the editors have translated into the Committee's approved terminology the designation used by the author cited. Although there may be certain underlying physiologic aberrations held in common by patients with these two great types of arthritis, the majority of workers are more and more convinced that the two types should be considered separately for the reasons noted above, for the sake of prognosis if for no other reason. Some still regard them as different expressions of the same disease, among them Knaggs,[197] Willcox,[198] and Clawson and Wetherby.[199] Wetherby [200] believes that both are forms of streptococcal arthritis, and has grouped both types together in a clinical analysis of 350 cases, in 69 per cent of which patients were women. Among points noted were that subcutaneous nodes were present in 31 per cent of 300 cases, and that roentgenograms revealed an "atrophic arthritis" in one joint, such as a shoulder, and a "hypertrophic arthritis" in a knee in the same case. (It would appear that part of the author's difficulty in separating types is failure to recognize the difference between the term "hypertrophic arthritis" when used in a radiologic sense,

and the same term when used in the clinical sense. Since no attempt was made by him to separate types, his figures cannot be compared with other series analyzed hereafter.—Ed.)

Roentgenography of Chronic Arthritis. In roentgenologic literature there is a tendency to divide arthritis into three groups, following Goldthwaite (1904): atrophic, hypertrophic, and infectious. Many have abandoned the third group on the ground that its radiologic characteristics were identical with those of atrophic arthritis. The typical roentgenographic alterations of atrophic and hypertrophic arthritis need no review here.[188]

Scott [201] distinguishes a third group, dividing hypertrophic arthritis into infectious and noninfectious types. Rigler and Wetherby [202] studied the roentgenograms of 564 joints of 60 patients with chronic polyarthritis, where pain or deformity was or had been present. Twenty-five per cent were radiologically negative; 31 per cent showed changes of atrophic arthritis, that is, atrophy of soft tissues and destruction of cartilage and bone, and fibrous ankylosis. No case with any degree of new bone formation was held to belong to this group. Twenty-three per cent of cases were classed as hypertrophic arthritis: with no atrophy of bone, no ankylosis, and little or no cartilaginous destruction. Twenty per cent were placed in the so-called "infectious" group, and were characterized by destruction of bone and cartilage and formation of new bone with or without ankylosis. While these latter cases appear to be mixed types, they were distinguished from the atrophic group by the presence of new bone formation and from the hypertrophic group by the presence of marked cartilaginous and bony destruction, and also by the character of the new bone formation. Hypertrophic changes were not seen in any elbow or shoulder but were largely confined to knees, spinal column, and sacro-iliac region. Few atrophic changes were seen in the knees and spinal column. The hands, normal in only 5 per cent of cases, showed atrophic arthritis in 45 per cent, hypertrophic arthritis in 9 per cent, and "infectious arthritis" in 41 per cent. After the fifth decade of life few joints were normal and hypertrophic changes predominated. Of 56 pathologic joints, 37 per cent showed one type, 52 per cent two types, and 11 per cent all three types of involvement. Frequently a joint affected more than five years was still roentgenologically negative. Noting that "infectious arthritis" appeared more often in those whose illness had lasted longer, or who were older, Rigler and Wetherby concluded that it was but an extreme phase of atrophic arthritis and agreed that the third classification should be abandoned.

(It should be noted that the separation was a radiologic and not a clinical one, that weight bearing joints were more prone to show hypertrophic changes, and that although many patients presumably had both types of radiologic arthritis that does not mean that many had both clinical types of arthritis. The criteria for "infectious arthritis" used by these authors were not the same as those used by Goldthwaite.—Ed.)

To determine the presence of adhesions in arthritic joints and the prob-

able value of manipulation Keller [88] visualizes them by the intra-articular injection of a yellow dye, "arthropsin," a 10 per cent solution of the disodium salt of tetra-iodo-ortho-sulpho-benzoic acid.

Atrophic Arthritis (Infectious, Proliferative, Rheumatoid)

Symptoms and Course. New series have been analyzed: 44 cases by Stecher [203]; 48 cases by Rawls, Gruskin and Ressa [204]; 102 cases by Smith [205]; 113 cases by Lipkin [206]; 172 cases by Matz,[21] and 173 cases by Eaton.[194] Analyses have been made of many details, among them sex incidence, hereditary and constitutional factors, presence of allergic phenomena among patients and their families, prodromes, age, various modes of onset and progression of the disease, and related disturbances of endocrine, vascular, gastrointestinal, and locomotor systems. In the main, the well-known picture of the disease is again portrayed. Here and there a shadow is clarified, a high light toned down, a feature sharpened.

The usual sex incidence, 1.5–2 women to 1 man afflicted, prevailed in Smith's and Lipkin's series. Matz' patients were all men, war veterans. In Smith's series there were 60 women and 42 men, in a former series 325 women and 287 men. In 38 per cent of his cases a family history of arthritis was obtained.

Factors of occupation played no definite rôle in either Smith's or Matz' series except perhaps in the case of a few minors. More patients were of the asthenic than the sthenic or intermediate type, but the disease was not limited to one anthropologic configuration. There was no significant correlation between the physical type and the onset of the disease, which seemed to affect brunettes more often than blondes, contrary to expectation. Loss of weight may begin early in the prodromal stage. At the onset of the disease about 36 per cent of Eaton's patients were underweight, 34 per cent obese. During their illness 63 per cent of Eaton's male patients, 48 per cent of his female patients, and 68 per cent of Matz' patients lost weight. The average loss of weight was 32 pounds in 18.5 months, with a maximal loss of 100 pounds in six months in one case (Smith). Some patients gained weight even during the course of their illness.

Smith stressed the importance of recognizing the prodromes which may be present for a year or more before the onset of symptoms in joints. The chief prodomes are fatigue and nervous irritability, but in addition there was a large variety of symptoms referable to the vasomotor, muscular, and sensory systems. When the disease is established, symptoms in bones are frequently present,—a point not well known. Circulatory phenomena are found: alterations in pulse rate, blood pressure, color, and in sensation and temperature of extremities, with erythemas, wheals, and other cutaneous manifestations. Moderate alterations in blood pressure were noted by all. In the majority of Matz' cases the pressure was normal, though some patients had moderate hypertension. The variations seemed to Eaton to be

as one would expect in any chronic disease, but both he and Smith, who noted evidence of hypertension in some and hypotension in others, remarked that regardless of which alteration was present there seemed to be a definite attempt on the part of the vascular system to maintain an adequate pulse pressure, either through lowering of the diastolic or elevation of the systolic pressure. As the arthritis improves, hypertensive subjects have a lowering of the blood pressure, particularly the diastolic; hypotensive subjects have an elevation of systolic and lowering of diastolic pressures.

The rarity of renal lesions and the relatively frequent secondary anemia were noted, the latter thought to be due to toxemia and poor appetite. While Matz noted no evidence of related allergic diseases, Lipkin and Smith noted it among patients and their families often enough for comment. Lipkin and Matz found no evidence of thyroid or other endocrine disturbance. Forestier [207] and Smith [205] found the metabolic rate generally to be normal. Smith is inclined to believe that these figures are " false-normals." Recalling that many of these patients had lost much weight, especially in fatty tissue, which has a very low metabolic rate, he considered it possible that where the oxygen consumption at basal levels compared with what it should be for the surface areas based on the weight and height of those patients before their loss of weight, it would be found that the result would be 10 to 20 per cent below normal.

(Many feel that the occasional disturbances of metabolic rate in atrophic or other types of arthritis may result from, rather than be the cause of, the disease. In this connection, thyroid changes noted by Alexandresco and Lautier (1931), in monkeys affected by experimental " infectious rheumatism " after injection of diplostreptococci are of interest. The thyroid changes varied with the intensity, duration, and kind of germ employed. A picture of hyperfunction was produced by attenuated germs after a short infection. With repeated and prolonged infection, a histologic picture of hypofunction resulted. Nodules resembling the Aschoff type were seen.—Ed.) Children whose arthritis lasts from 2 to 15 years may, according to Kuhns and Swaim,[208] develop marked disturbances of growth, the order of frequency being persistence of infantile proportions of hands and feet, asymmetrical development, and dwarfism. While this is favored by non-use and by nutritional and endocrine dysfunction, it is chiefly due to involvement of the proliferating epiphyseal cartilage, resulting in early ossification, and is dependent on the severity and chance location of the arthritis.

Studies on Pathology; Joints. Three monographs serve as the basis of our knowledge of the pathology of articular tissues in atrophic and hypertrophic arthritis: that of Nicholls and Richardson (1909), of Pommer (1913), and of Allison and Ghormley (1931). The last named is to date the most complete study on pathology related to clinical, chemical, and roentgenologic data. Allison and Ghormley (1931) confirmed findings of previous writers, and in addition noted focal collections of lymphocytes in bone marrow and synovia. The last two regions are always attacked

first, and changes in bone and cartilage were secondary to those in marrow and synovia. Brief synopses on pathology of both principal types of arthritis were presented by Eaton.[209]

All these writers agree on the essential pathologic distinctness of the two types. From an extensive study of the Strangeways collection, Knaggs [197] has concluded that there is no sharp dividing line between atrophic and hypertrophic arthritis. He reported a frequent finding, in cases of atrophic arthritis, of eburnation and extensive marginal lipping, characteristics presumably reserved chiefly for hypertrophic arthritis. On the other hand, ankylosis, not only of the spine but also of carpal and tarsal joints, was frequently exhibited in cases of hypertrophic arthritis. Others have said that, aside from that in the spine, ankylosis does not occur in cases of hypertrophic arthritis. In many specimens features were present on which a diagnosis of either type could be made. Knaggs argues, therefore, that both types "are expressions—at the opposite ends of the same scale—of a single disease," which he believes arises from one toxin, either microbic or otherwise. They are not separate affections but simply names by which two groups of characteristic pathologic changes are distinguished. The two types are, it is true, often distinctive pathologically, but they represent differing reactions, probably to the same insult, which are dependent on "the vitality of the joint tissues and ability to resist or modify the reaction that toxic damage may excite." Knaggs reflects on the fact that patients with hypertrophic arthritis are usually robust and healthy, and that atrophic arthritis is more likely to attack the delicate and feeble. Thus he concludes that "when the tissues are healthy and robust the toxic irritation acts as a stimulus to growth processes and osteo-arthritis results. When the vitality of the tissues is poor, inflammatory reaction may be excited, but in the event that the affected tissues are unable to maintain their vitality in the face of such reaction, degeneration or even disintegration results. In either case, rheumatoid arthritis develops." (This interesting paper would be much more forceful if clinical data had been presented with the pathologic data. The reader could then see how often and to what extent a clinical history of atrophic arthritis was associated with the pathologic findings presumably characteristic of hypertrophic arthritis, and vice versa. Such clinical data, according to Knaggs, are available and should be utilized to strengthen the argument, which otherwise seems somewhat weak if we recall, with Smith,[205] that atrophic arthritis is confined to no one physical habitus and often appears in the sthenic, robust type.—Ed.)

Subcutaneous Nodules.—Present in 10 to 25 per cent of cases of rheumatic fever, subcutaneous nodules have been thought to be less common in cases of chronic arthritis. According to Clawson and Wetherby,[210, 211] and Dawson and Boots [212, 213] they occur as frequently, if not more so (20 to 30 per cent), in cases of chronic arthritis, and they are likely, furthermore, to be larger than in rheumatic fever. Dawson and Boots found them only in atrophic arthritis, never in hypertrophic arthritis in spite of diligent

search. They believe that their consistent absence in the latter is one more point in favor of the contention that hypertrophic arthritis is an entity distinct from atrophic arthritis. Clawson and Wetherby, without separating types, found such nodules in many cases which they think would be called hypertrophic or degenerative arthritis by others. Thus they described subcutaneous olecranon nodules in a case in which the patient, a woman 75 years old, had for five years been having pain and stiffness in "toes, ankles, knees, right hip, fingers, wrists and cervical spine," in all areas of which, except the ankles, which were negative, roentgenographic examination showed "hypertrophic arthritis." (It would seem that these authors do not fully appreciate the difference between a clinical and a roentgenologic diagnosis of "hypertrophic arthritis." This patient at 75 undoubtedly had senescent (hypertrophic) arthritis, as everyone at that age has. Strangely, however, senescent (hypertrophic) arthritis practically never involves toes or ankles, and the wrists practically never show radiologic change or even clinical symptoms aside from minor pains. The patient with that many joints involved undoubtedly had infectious (atrophic) arthritis also, and if the hypertrophic changes were present in all the joints as noted, some of them probably represented the hypertrophic bone reactions of fairly well-advanced infectious (atrophic) arthritis.—Ed.)

All of these workers agree that the gross and microscopic lesions seen in these nodules are essentially similar to, if not identical with, those of nodules in rheumatic fever, and that they bear no relationship to those seen in yaws, gout, syphilis, or tuberculosis. It is further agreed that their common presence in rheumatic fever and atrophic arthritis suggests a close relationship between these two diseases.

Laboratory Data: Blood Counts, Blood Volume, Blood Chemistry. The nonfilament count was found by Steinbrocker and Hartung [214] to be elevated in 100 per cent of 50 cases of atrophic arthritis. It was normal in 52 per cent and elevated in 48 per cent of 50 cases of hypertrophic arthritis. When it was elevated in cases of hypertrophic arthritis, the average elevation was less (22.3 per cent) than in cases of atrophic arthritis (31.5 per cent). When the count is normal (nonfilament count 15 per cent or less), the patient in all likelihood does not have atrophic arthritis. When it is elevated, he may have either type: if it is markedly elevated in all probability his arthritis is of the atrophic type.

In 250 undifferentiated cases of "chronic arthritis" Eaton [215] found only three with normal blood counts. Characteristics were slight secondary anemia, normal or slightly low leukocyte counts, a tendency toward lymphocytosis, eosinophilia in 10 per cent of the cases (highest eosinophile count 9 per cent) and the appearance of juvenile cells causing in 90 per cent of cases a nuclear shift to the left in a Schilling hemogram. To Cecil [216, 217] the presence of immature polymorphonuclear cells suggested infection above all else.

The blood volume of 26 patients with atrophic arthritis whose average

weight was normal was found by Sparks and Haden [218] to be 12 per cent above the normal average, the increase being due entirely to an increase in plasma. Since it is assumed that in spite of this the joints are receiving a poor blood supply, it may be deduced that the excess volume is held in splanchnic vessels. If so, the beneficial effect of breathing and postural exercises is explainable.

A review of the literature on the chemistry of the blood in both types of arthritis is presented by Eaton and Cocheu [219] in addition to studies in 304 cases in which 183 were of the atrophic and 121 of the hypertrophic type. In both types the values for blood sugar, urea, and creatinin, were essentially normal. There was a tendency toward a moderate increase in blood uric acid,—in a number of each type there were values between 4 and 5 mg. Values more than 5 mg. per 100 c.c. were found in only two cases of atrophic and in four of hypertrophic arthritis. No significant changes in serum calcium or serum phosphorus or in calcium and phosphorus metabolism were discovered by Bauer, Bennett, and Short [220] either in cases of atrophic or of hypertrophic arthritis.

The phosphatase test was found by Race [221] to be normal in 10 cases of atrophic and in 11 of hypertrophic arthritis, and it was also normal in nine cases of fibrositis and in two of gout. It is likely to be slightly elevated in spondylitis of the ankylopoietic type, and it is generally abnormal in types of osteitis, often reaching values five to ten times that in the arthritides. Race concluded that the phosphatase content is normal in diseases in which joint structures only are significantly involved.

Many (e.g. Cecil [217]) have noted that the sedimentation of erythrocytes is more rapid in atrophic than in hypertrophic arthritis. In atrophic arthritis it is usually above 30 mm. in one hour (Dawson and Boots [213]; Rawls, Gruskin and Ressa [204]) and parallels to an extraordinary degree the severity and extent of the arthritic process. In hypertrophic arthritis the rate is usually normal (less than 10 to 15 mm. in one hour); although it is occasionally 20 to 30 mm. it is rarely above that value. Thus the test will help to differentiate the two forms. The rate is also elevated, however, in gonorrheal, gouty, and tuberculous arthritis; it is normal in fibrositis and neuritis.

The average figure for the sedimentation rate at the end of one hour in atrophic arthritis is 42 mm., according to Forestier [207]; in 16 per cent of cases it is between 10 and 20 mm., in 20 to 30 per cent between 20 and 30 mm., in 30 per cent between 30 and 50 mm., in 26 per cent between 50 and 80 mm., and in 5 per cent between 80 and 120 mm. While the sedimentation rate generally varies with the clinical course of atrophic arthritis and decreases as the patient improves, in some cases it remains elevated in spite of clinical improvement, according to Oppel, Myers and Keefer.[62] Single estimations are of little value, but repeated observations may give information of prognostic significance.

Kling [222] has developed a method for the comparative estimation of the

sedimentation rate of blood corpuscles in synovial fluid and plasma by replacing the plasma with equal volumes of fluid. The severity of infection in a joint is better illustrated by the sedimentation of corpuscles in synovial fluid than in the blood, the rate in the latter reflecting the general bodily reaction rather than the articular reaction. Thus in a case of monarthritis, if the rate in synovial fluid is low but that of the blood is high, some other infection than that in the joint should be considered responsible for the rapid sedimentation rate. A more accurate differentiation can be made between atrophic and hypertrophic arthritis if one has the opportunity of studying the sedimentation rate and viscosity of synovial fluid. Noninflammatory fluids with a low protein content have a low comparative sedimentation index and a low viscosity. Fluids with a high content of mucin show a low comparative sedimentation index but a high viscosity.

Electrocardiograms. Master and Jaffe [117] found only the slightest evidence of myocardial involvement by means of electrocardiographic examination of 17 patients with atrophic arthritis. In acute rheumatic fever, abnormalities were found consistently. A normal electrocardiogram would thus speak for the former in attempting a laboratory differentiation between acute or subacute atrophic arthritis and rheumatic fever.

Etiology and Pathogenesis of Atrophic Arthritis. An appreciation of differing views on the etiology of rheumatic fever will partially suffice to explain those regarding atrophic arthritis, since the same general diversity of ideas also relates to the latter. Theories on the cause of atrophic arthritis can be grouped under four headings: (1) infectious, (2) metabolic, (3) endocrine, and (4) neurogenic. The same variants of the infectious theory are held as for rheumatic fever. In atrophic arthritis the other theories, especially the metabolic, have more support than in rheumatic fever. The speculative literature in this field is voluminous and is not subject to review here. Several comprehensive considerations have appeared recently. (Eaton [194]; Cecil [217]; Bauer, Bennett and Short [220]; Pemberton,[223] Osgood,[19, 187] Dawson and Boots [213]; Clawson and Wetherby,[199] Miller,[133] Burbank,[224] Key [36]).

The Infectious Theory. This theory has three chief variants: the bacterial, the protozoal, and the virus. Some (e.g. Kendall, 1931) would add a fourth variant,—causation of the disease by a mutation form, which is not merely a mutable streptococcus but an organism that may become a virus on suitable mediums. The latter variant has been sharply challenged and has not received confirmation.

Bacterial Variant. The bacterial variant has the same three subvariants which were discussed under rheumatic fever: (1) the bacteremic idea of direct infection from focus, through blood to affected tissues, (2) the idea of bacterial toxemia and (3) the idea of bacterial allergy. Essentially the same type of schema (table 4) can be erected for atrophic arthritis as was displayed for rheumatic fever (table 2). In many of the brackets the same names can be appended, sometimes with minor variations,—a different strep-

TABLE IV

Bacterial Variants of the Infectious Theory of Atrophic Arthritis

(The names are representative only)

I. *Bacteremic variant.*

(*a*) Group specific: one type of organism held responsible.

1. Staphylococcus: Crowe (1927) *Staphylococcus albus,* "micrococcus deformans."
2. *Streptococcus hemolyticus:* Gray, Fendrick, Gowen (1932). Cecil, Nicholls, Stainsby (1929).
3. *Streptococcus viridans:* Clawson, Wetherby (1932).
4. Streptococcus, indifferent.

(*b*) Not group-specific: more than one type considered potentially responsible.

Streptococcus viridans (generally): Rosenow (1914).
Staphylococcic more often than streptococcic: Key (1929).
Streptococci, diphtheroids: Ashworth (1932). Strauss (1932).
Streptococcus hemolyticus and *viridans:* Hadjopoulos and Burbank (1932).
Pleomorphic: Cadham (1932).

II. *Toxic variant:*

(*a*) Group (and strain) specific:
Streptococcus cardio-arthritis: Small (1927).

III. *Allergic variant:*

(*a*) *Group specific:*

1. *Streptococcus hemolyticus:* Dawson, Olmstead, Boots (1931).
2. Other organisms.

tococcus, perhaps, being incriminated. Similar bacterial and immunologic investigations provide the basis of the arguments (table 5). Many who were able to obtain striking results in blood and tissue cultures and agglutination tests in rheumatic fever also obtained unusual results in atrophic arthritis, but the data are about as inconclusive, as open to varied interpretation, and as subject to critical debate as those in the case of rheumatic fever.

The reasons for the various conclusions are obvious. If an investigator finds bacteria in a significant number of foci and the same type of germ frequently in blood and affected tissues, the chain of circumstance seems complete in favor of the bacteremic theory. If blood cultures are repeatedly negative, yet the patient presents certain immunologic reactions that seem to be peculiar to an infectious disease (the property of agglutinating one or more organisms in high titer, hyperactive skin reactions, and so on), and if the observer further considers the pathologic changes in affected tissue to be consistent with an infection, it seems reasonable to conclude that infection is the cause but that it operates either through its toxins or bacterial antigens to which tissues are hypersensitive. When so many different germs are isolated from blood and when skin reactions and agglutination tests are not uniform, the germs under consideration must either be considered unrelated invaders or one is forced to favor the allergic hypothesis. To date no one variant is proved.

Blood Cultures. Reviews of the bacteriology of blood in atrophic arthritis have been made by several, among them Cecil.[216] (Bernhardt and Hench (1931) found that up to 1932, at the hands of all workers and by

TABLE V

INFECTIOUS THEORY OF ATROPHIC ARTHRITIS

Basis of approval of bacterial subvariants

(The names are but representative)

Test		Result
Culture of blood	(*a*) *Characteristic:*	(1) Group specific: attenuated hemolytic streptococci—Cecil, Nicholls, and Stainsby (1929), Gray, Fendrick and Gowen (1932). Pleomorphic form (bacillary and diplococcal)—Traut (1933).
		(2) Not group specific: various streptococci and diphtheroids—Ashworth (1932), Strauss (1932).
	(*b*) *Not characteristic:*	(Generally negative) Burbank and Hadjopoulos (1927); Kracke and Teasly (1932); Nye and Waxelbaum (1930); Margolis and Dorsey (1930); Bernhardt and Hench (1931); Dawson and Boots (1932); Ashworth (1932); Lichtman and Gross (1932).
Culture of joint tissues	(*a*) *Characteristic:*	(1) Group specific: attenuated hemolytic streptococci—Cecil, Nicholls, and Stainsby (1929); Gray, Fendrick and Gowen (1932)—"alpha prime."
		(2) Not group specific: *Streptococcus viridans* and indifferent—Rosenow (1914). *Streptococcus viridans* and (or) *hemolyticus*—Billings, Coleman and Hibbs (1922); staphylococci and streptococci—Key (1929).
	(*b*) *Not characteristic:*	(Or generally negative):—Forkner, Shands, Poston (1928); Margolis and Dorsey (1930). Nye and Waxelbaum (1930); Dawson, Olmstead, Boots (1932).
Agglutination	(*a*) *Characteristic:*	(1) Group (but not strain) specific: *Streptococcus hemolyticus*—Cecil, Nicholls, Stainsby (1931); (attenuated *Streptococcus hemolyticus*—Dawson, Olmstead, Boots (1932); Gray, Fendrick, and Gowen (1932). Ashworth (1932); Myers, Keefer, Oppel (1933).
		(2) Not group specific: staphylococci and streptococci—Crowe (1924).
	(*b*) *Not entirely characteristic:*	*Streptococcus viridans* and *hemolyticus*—Clawson and Wetherby (1932). Agglutinins also possessed by controls, but in lower titer.
Skin sensitivity	(*a*) *Characteristic:*	(1) Group specific: *Streptococcus viridans*—Clawson, Wetherby (1932).
		(2) Not group specific: *Streptococcus viridans and hemolyticus*—Birkhaug (1929), Lautman (1932).
	(*b*) *Not entirely characteristic:*	Pilot (1932); Myers, Keefer, Oppel (1933).
Complement fixation (streptococcal)	(*a*) *Characteristic:*	Hastings (1913). Burbank and Hadjopoulos (1925). Crowe (1925); Munro (1925).

Culture of lymph nodes	*Generally positive:*	*Streptococcus viridans*—Rosenow (1914). Forkner, Shands, Poston (1928). Pleomorphic (bacillus-diphtheroid-coccoid)—Cadham (1932).
Culture of subcutaneous fibrous nodes	*Generally positive:*	*Streptococcus viridans* (diplococcus)—Clawson and Wetherby (1932).
Culture of stools	*Generally positive and characteristic:*	Crowe (1927); Burbank (1932); Vaughan (1932).
	Negative:	Dawson and Boots (1932).
Experimental arthritis	*Generally positive to suspected organisms:*	Rosenow (1914); Cecil, Nicholls, Stainsby (1931). Hadjopoulos and Burbank (1932). Cadham (1932).

different methods, a total of about 780 cases had been studied. In 74 per cent blood cultures were sterile. Various organisms were isolated in 26 per cent. Streptococci of various types (generally viridans) were isolated in only 18 per cent. Organisms other than streptococci were found in the remaining 8 per cent. The percentage of positive cultures obtained by different workers varied tremendously, from 69 per cent to none, the highest being that of Cecil, Nicholls, and Stainsby (1929).—Ed.)

Several recent additional studies are reviewed. By a modification of Cecil's method, Gray, Fendrick and Gowen [107, 108] isolated streptococci "from the blood or joint fluid or both" in 61 per cent of 144 cases. The organisms were of the alpha (viridans) or alpha prime type in 95 per cent of the cases, and of the gamma (hemolytic) type in 5 per cent. Those isolated in atrophic arthritis were only very slightly different from those found by them in 71 per cent of 28 cases of rheumatic fever.

Ashworth [225] and Straus [226] found various organisms in the blood in 41 per cent of 138 cases. In 28 per cent of 39 cases an organism resembling the "typical strain" (attenuated hemolytic streptococci) of Cecil, Nicholls and Stainsby was found. In 13 cases a diplococcus was found. There was considerable pleomorphism noted in subcultures, many streptococci being at first considered diphtheroids. Straus believed both the diphtheroids and the streptococci to be of etiologic importance, and he favored the multiple streptococcal (and multiple bacterial) theory as against a single etiologic species. A pleomorphic type of organism was isolated by Traut [227] from the blood in 71 per cent of 38 cases. It was primarily a bacillary or diplococcal form, although some were coccoid forms in chains. Clawson's technic was used. Traut emphasized the fact that to obtain positive blood cultures successfully, prolonged cultivation and the recognition of the likelihood and importance of pleomorphism and dissociation is necessary. (Animal experiments are not mentioned in these four reports and no evidence is given that the organisms isolated were arthrotropic.—Ed.)

No significant organisms could be found by Haden,[228] by Dawson, Olmstead, and Boots,[229] who made 105 blood cultures in 80 cases using the method of Cecil, Nicholls, and Stainsby, or by Lichtman and Gross,[230] who

studied 48 cases. Different organisms were isolated in a small percentage of cases, but they were similar in type and frequency to those from controls. The study by Lichtman and Gross of 5,233 consecutive blood cultures in a general hospital showed that, with adequately sensitive methods, an incidence of nonhemolytic streptococcemia (alpha and gamma types) between 4 and 15.5 per cent (average 6 + per cent) occurs in at least nine different diseases, and that on the basis of the incidence of the transient bacteremia alone, these organisms cannot be considered of etiologic significance.

Agglutination Tests. These tests have given more uniform results, and it may be significant to note that whereas in the past *Streptococcus viridans* has been considered the most likely offender, suspicion is now being cast more on hemolytic streptococci. The findings of Cecil, Nicholls and Stainsby (1931) have apparently been confirmed by several groups of workers. Although Dawson, Olmstead, and Boots recovered no significant organisms from blood, they [231] found that the serums of the majority of patients with atrophic arthritis possessed the property of agglutinating several strains of hemolytic streptococci to an extraordinarily high titer. Tests with a number of other organisms revealed little or no agglutination except to R pneumococci, which were agglutinated to almost as high a titer as the hemolytic streptococci.

Agglutination tests to hemolytic streptococci were positive in 74 to 80 per cent of the cases of atrophic, but in no case of hypertrophic arthritis seen by Gray, Fendrick, and Gowen. Ashworth, using Cecil's strain, noted positive results in 89 per cent of 65 cases of atrophic, but in none of 100 cases of hypertrophic, arthritis. Keefer, Myers and Oppel,[140] using four strains of hemolytic streptococci, found that 55 per cent of 22 patients with atrophic arthritis and 15 per cent of 28 patients with hypertrophic arthritis had positive serum agglutinins. There was no evidence of strain specificity, nor were they correlated with an unusual sedimentation rate or positive skin reactions to nucleoprotein of hemolytic streptococci. They and Dawson, Olmstead and Boots agreed that the reactions differ from the type which, as Tillett and Abernethy [141] showed, occurs in certain febrile human serums. It is also agreed that reactions do not become significantly positive for several weeks after the onset of the disease, and that they depend, in part, on the severity of the arthritis. Dawson, Olmstead, and Boots felt that their presence is related to the duration of the disease and the age of the patient, an idea to which Nicholls and Stainsby [231a] could not agree. Haden [228] was unable to find agglutinins to *Streptococcus viridans,* and, although those to hemolytic streptococci were frequently obtained, they were also found in a high percentage of control cases. He therefore doubted their significance.

The significance of these reactions is but little understood.[232] They are thought to suggest, but not to prove, some etiologic relationship between arthritis and the organisms involved. As the disease recedes, titers generally fall and tests become negative. Clawson and Wetherby believed that they rise higher in patients to whom streptococcal vaccine is given intravenously

than in those treated subcutaneously, and are an evidence of developing immunity. Fletcher [233] however, insists that a rise in blood agglutinins does not always indicate favorable change. Whatever their significance agglutination tests will apparently differentiate atrophic and hypertrophic arthritis.

Cutaneous Tests. Intradermal tests were performed by Clawson and Wetherby,[200, 210, 211] using a green streptococcus. More arthritic patients (types not separated) gave positive reactions thereto than did controls, but the reactions in a given case were of little significance. Anderson [234] and Pilot [235] were unable to get consistent reactions with dilute toxins of hemolytic or other streptococci. Lautman [236] considers such reactions of some diagnostic significance. Others, while admitting that they apparently indicate a hypersensitivity of the particular person to the organisms used, believe the evidence that there is some relationship between the disease and the organisms that produce the skin reaction is by no means conclusive. (Clawson and Wetherby [199]; Myers, Keefer and Oppel.[237]) It has been claimed that in certain allergic diseases, a substance, probably a proteose, can be isolated from the patient's urine which, when injected intradermally, gives a skin reaction similar to the reaction of antigen in an allergic patient sensitized to that antigen. It has also been stated that a flare-up of joint manifestations can be brought out thereby in certain cases of atrophic arthritis. Aldred-Brown and Munro [238] prepared autogenous urinary vaccines in 50 cases. In all cases skin tests were negative to scratch and patch tests. Six patients were treated with weekly injections of proteose; five were not relieved.

Cultures of Joint Tissues. Streptococci were frequently isolated from joint fluid by Gray, Fendrick, and Gowen, as noted. No significant organisms were found by Dawson, Olmstead, and Boots in aerobic and anaerobic cultures of 23 specimens of synovial fluid.

Cultures of Lymph Nodes, Fibrous Nodules, and Stools. From 27 of 34 regional lymph nodes, Cadham [239] isolated a diphtheroid with pleomorphic characteristics. Primary cultures, which took 14 to 21 days to develop, were sometimes a coccoid type resembling minute streptococci, with bacillary forms in subcultures. Arthritis was experimentally produced in rabbits. He believed they were probably identical with organisms originally isolated by Schüller (1892), from nodes by Rosenow (1914), and occasionally from blood by Burbank (1925).

A diplococcus or *Streptococcus viridans* was isolated from subcutaneous fibrous nodules cultured by Clawson and Wetherby. No attempts to produce experimental arthritis are recorded. Although Dawson, Olmstead and Boots [229] recovered no organisms from such nodes on culture, their appearance was that of an inflammatory granuloma, and their structure was highly suggestive of an infectious process.

The isolation of presumably significant organisms in feces has been further reported on by Vaughan,[240] Meader,[241] Burbank,[224] and Traut.[242]

Allergic Diseases and Arthritis. To lend support to the theory of bacterial allergy, inquiries have been made regarding the coexistence of arthritis with diseases thought to be allergic. Such diseases were found by Aldred-Brown and Munro in only two of 50 patients with atrophic arthritis and in only one of their families. Harkavy and Hebald [243] noted among 400 patients with asthma only nine with arthritis. Elimination of atopens to which they were clinically sensitive relieved neither the asthma nor the arthritis. The treatment of sinus and ethmoid infections was followed by complete subsidence of the arthritis in eight of the nine cases, with some relief of the asthma also. Rackemann [244] rarely found a history of "rheumatism" in patients with asthma and hay fever.

Allergic Theory and Experimental Arthritis (Synovitis). Several have produced arthritic changes by sensitizing animals to bacterial or nonbacterial proteins and then injecting the antigen into joints. Similar results have been obtained if the antigen was injected into joints, later into the blood. Brunschwig and Henry [245] questioned whether these changes were allergic or due to other factors. Their experiments indicated that while acute and chronic inflammatory changes in synovia and adjacent tissues can be produced by products of bacterial decomposition and metabolism (filtrates of various bacteria), almost identical reactions are produced by such foreign proteins as egg white and human blood serum. They consider them the result of a direct action of foreign proteins on synovia rather than an allergic phenomenon. The early eosinophilia noted does not necessarily indicate allergy but may be accounted for by the soluble nature of the noxious agents used, since eosinophiles are cells of defense against soluble toxins.

Comment on the Infectious Theory. Only a few of the workers who have attached etiologic significance to certain organisms have determined their arthrotropic potentialities to the extent of trying to produce experimental arthritis in animals. Of the more recent workers, Cecil and his colleagues, and Hadjopoulos and Burbank [246] produced subacute and chronic arthritis with clinical and pathologic features considered identical to those of atrophic arthritis. The organisms injected were recovered from the blood and many of the tissues of the affected animals. Such experiments have been vital to the idea of a bacteremia and direct bacterial infection; but they are laborious and expensive. Nevertheless, it is unscientific to attribute pathologic properties to an organism, and useless to make an "autogenous vaccine" therefrom just because it happens to be located in an arthritic patient's stool, throat, or other "focus." Much of the strength of the streptococcal theory has been vitiated by arguments over the cultural differences in organisms isolated. Much of the worth of vaccine therapy has been discounted because "autogenous vaccines" have failed to help, vaccines made from organisms utterly unrelated to the patient's disease.

Bacteriologists are too much concerned with differences in cultural reactions and not enough with determining the pathologic propensities of the streptococci isolated—their tropism or peculiar infecting power. The re-

quirements of some, that all streptococci isolated must have identical cultural reactions to be of significance, is fallacious, according to Rosenow [247] who has shown by a long series of experiments that streptococci isolated in cases of chronic arthritis, irrespective of whether they were green producing, indifferent, or slightly hemolytic, possess peculiar localizing and disease producing powers. Of such organisms, arthrotropism was exhibited in 53 per cent of 1,447 animals injected therewith, with invasion of other tissues in much smaller (1 to 8 per cent) numbers.

The estimation of the electrophoretic potential of different organisms presents a new and simple method for determining their pathogenic properties without the difficulties of other and older methods. Bacteria, in the presence of an electric field, act as ions and carry a negative charge. Cultures of suspected foci are inoculated into warmed glucose brain-broth and incubated overnight. The top two c.c. of the culture are poured off into a scrupulously clean test tube and centrifuged for 10 minutes. The sedimented bacteria are suspended in 12 c.c. of distilled water. This suspension is then poured into an electrophoresis apparatus, of the Northrup-Kunitz-Mudd type, and under standard voltage and other standard conditions the rate of 20 or more streptococci is determined by noting, with a stopwatch, the number of seconds required for the germs to travel a unit distance of 32 microns. The higher the charge, the faster is the rate of travel toward the positive pole. Streptococci, which repeated animal experiments show to be arthrotropic, have their own rate of migration. Neurotropic organisms have a different speed of migration. The velocity of normal saprophytes and of many types of organisms has been established; that of arthrotropic organisms, for example, is chiefly 2.22 microns per second per volt per centimeter. The blood serum in cases of atrophic arthritis has a slowing effect on the rate of migration, far greater than the serums of encephalitic or poliomyelitic patients have in slowing "neurotropic" organisms. Adsorption experiments with arthrotropic streptococci removed specifically from the serum of patients with arthritis this power of reducing velocity. These investigations, Rosenow feels, explain much regarding the mutability of streptococci and the conception of elective localization. It is much more important to study and to try to alter a germ's habits regarding disease production than its habits of color production on mediums. The latter can be changed without always changing the former, and vice versa. Using this method, which is of great diagnostic help, it is no longer necessary to inject cultures from atria of infection intravenously into animals and to make cultures from their joints in order to be certain that the streptococcus isolated may be etiologic. According to Rosenow the determination of the cataphoretic velocity will usually suffice.

Other Theories on the Cause of Atrophic Arthritis. There have been no important additions to the data on which the parasitic or virus variant of the infectious theory was based. (In regard to the idea advanced by Ely,[248] Barrow [249] and others, that arthritis might be related to an ameba, it may be

significant to recall that arthritis is not so far a reported complication or aftermath of the Chicago epidemic of amebiasis in 1933.—Ed.) New evidence in support of the endocrine, metabolic, and neurogenic theories will be discussed together, since proponents who formerly were inclined to incriminate one system, such as the endocrine, now generally believe that an interrelated disturbance may be responsible for arthritis. Thus they speak of disturbances of the "endocrine-sympathetic system and the chemical and metabolic alterations associated therewith." Those who do not accept the primary importance of bacteria in the production of atrophic arthritis generally believe that the predisposing factor is an inherent physiologic weakness. The precipitating factor may or may not be an infection, but the main factor is some as yet undiscovered metabolic disturbance, some alimentary toxemia, more likely to be chemical than microbic.

There are several variants to each of these theories: of the endocrine, that it is a disturbance of thyroid metabolism, of the parathyroid, suprarenals, ovaries, or other endocrine glands, alone or in combination. Variants of the metabolic or chemical theory are that the disease is due to (1) a perversion of food chemistry, (2) food allergy, (3) vitamin deficiency. Disturbances in the utilization of carbohydrates, of calcium, magnesium, or phosphates, and of sulphur, have all been suspected. Eaton [194] has reviewed current data on these ideas.

It is generally agreed that the soil in an arthritic patient is probably peculiarly altered to permit the later development of the disease. The tendency to asthenia, inadequate circulation, and poor thermo-regulation are signs of an inherent weakness or "rheumatic diathesis," which Llewellyn [158, 159] and Jones [161, 162, 250] have long thought to be due to hypothyroidism. They believe that the storage in skin of amino acids, tyrosine, and cystine may be of fundamental and etiologic importance. Tyrosine is the mother substance of which the thermo-regulating hormones, thyroxine and epinephrine, are chemical derivatives; and also of melanin. Tyrosine enters into the formation of insulin, another heat-producing hormone, and the sulphur content of insulin is derived from cystine. These writers suggest that ultra-violet rays may be of value in arthritis because they increase the tyrosine, and hence potentially the thyroxine and epinephrine in blood.

Thyroid Dysfunction and Arthritis. The appellations "endocrine rheumatism" or "menopause arthritis" refer generally to the hypertrophic form, but disturbances of thyroid or ovarian function are held by some to be an important, if not the main, cause of atrophic arthritis also. Continuing his earlier study (1928) on the relationship of thyroid disease to chronic arthritis, Duncan [251] reported cases in which severe joint pain lessened markedly following thyroidectomy for hyperthyroidism. Either form of preëxisting arthritis may be aggravated by a metabolic variation in thyroid function above or below the normal level, but especially by hyperthyroidism. Especially can relief be given by thyroidectomy in cases in which articular pain has appeared during the course of the hyperthyroidism. Such cases

Duncan is inclined to group separately,—joint pains being due neither to "atrophic" nor "hypertrophic arthritis" but to hyperthyroidism itself. In such cases pain was referred to one or both shoulders, with involvement of the hands, particularly on the side on which the shoulder was implicated. Generally, the pains were not relieved by usual measures, including bed rest, but marked relief was frequently experienced within a few hours after thyroidectomy. (Since the joints continued to improve, one infers that the relief was not of the temporary nonspecific type that an arthritic patient may experience after almost any surgical experience.—Ed.) Hypothyroidism is more likely to be associated with slowly progressive, degenerative articular changes. They are in part relieved by thyroid administration.

Four patients with advanced atrophic arthritis and with elevated metabolic rates (+ 18 and + 16, + 60, + 25, + 35) were seen by Lautman.[252] The appearance of the first patient was so suggestive of hypothyroidism rather than hyperthyroidism that small doses (¾ grain) of thyroid extract were given for 10 days, after which the metabolic rate had fallen to — 10 per cent, rather than increased. On the basis of this experience, thyroid extract was given to the other three patients also. In each case the paradoxical reaction of a lowering of the rate was noted. (The author speculates on the reasons therefor. In only one of these cases was the initial metabolic rate checked. One wonders whether the rates given were really basal, and whether the thyroid preparation was active or absorbed. The presentation of such a paradoxical reaction, noted after repeated estimations of the rate, to extracts of proved potency or to injected thyroxine would be of considerable interest.—Ed.)

Pemberton [253] early noted that the metabolic rate of many arthritic patients is lowered, not because of difficulty in combustive processes alone but from a condition of vasoconstriction in finer vessels, especially in muscles, which induces a relative anoxemia or anemia resulting in dysfunction of tissues in which the combustive processes are initiated. In 36 per cent of 106 cases of atrophic arthritis Hall and Munroe [254] found rates below — 10 per cent. In 18 per cent of cases it was below — 17 per cent. The lowered rates were thought to be due to enforced inactivity. Signs and symptoms of hypothyroidism were seen less frequently than in hypertrophic arthritis. They concluded that thyroid deficiency was not so important a factor in atrophic as it may be in hypertrophic arthritis, but that, when present, its correction may be helpful in a small (17 per cent) number of cases. The basal metabolic rates were normal for all but eight of 65 patients with "chronic arthritis" seen by Martin.[255] In the eight cases the rate was below — 20 per cent.

Alterations in Nutrition and Blood Chemistry. The opinion of those who favor the metabolic theory is that bacteria play only a minor (perhaps precipitating or complicating) rôle, and sometimes none at all, in the production of atrophic arthritis, and that some metabolic error, arising from a disturbed alimentation and circulation, is the causal factor in producing

the disease among persons who have inherited or acquired the proper soil therefor. Pemberton believes that 50 per cent of all patients inherit a background characterized by an asthenic body build, instability of the nervous and vasomotor system, and lack of intestinal tone. It is on such a soil that arthritis becomes engrafted as the direct result of some as yet unidentified toxic agent. Such a chain of events is manifested by many obvious chemical and physiologic aberrations, some of which can be corrected with benefit to the patient. The chief proponents of this theory are Pemberton, and his colleagues, and Osgood, in the United States, and Fletcher,[256] in Canada. Their writings are too well known to need review here.[257] Fletcher, and Pemberton and Peirce [258] again note the frequency with which arthritis of both types is accompanied by enlargement and tortuosity of the large bowel. Sometimes the condition is congenital, sometimes acquired. Once established, it may be an aggravating factor in some cases of arthritis, an original exciting factor in others. They believe that the use of a diet low in carbohydrates and calories, and high in vitamins, especially vitamin B, may be followed by a complete or partial restitution of the intestinal abnormality and by considerable cessation of arthritis. Such treatment must be applied, however, only in appropriate cases, and only on the basis of familiarity with the principles concerned. (While Fletcher and others have produced atonic bowels in rats which were given inadequate amounts of vitamin B, so far no definite arthritis has been produced in any experimental studies with foods or vitamins in deficient or excessive quantities.—Ed.)

Considering that the cecum is the source of absorption of most of the bodily fluids, Barrow [249] feels it is highly probable that toxins responsible for arthritis are elaborated therein and absorbed therefrom. Such toxins may be of several sources: from dissolution of body cells, bacterial endotoxins and exotoxins, abnormal food chemicals, and possibly also toxins either elaborated by, or resulting from, lysis of protozoa, the presence of which he feels is more than coincidental.

The changes in the colons of 25 patients with "chronic arthritis" (undifferentiated) and 25 controls ("average dispensary group") were studied by Haft.[259] Incompetency of the ileocecal valve was found in 80 per cent of the arthritic patients, and in 16 per cent of the controls; lack of haustration in 64 per cent and 78 per cent; atony in 40 per cent and 8 per cent, and redundancy in 85 per cent and 80 per cent, respectively. Thus Haft concluded that these intestinal changes were not typical of arthritis but could be found in any chronic disability associated with malnutrition and inadequate diet. Any one of these variations may occur without symptoms. They may be the result, not the cause, of disease, but their correction may be helpful. Repeated fluoroscopic examinations of the colons of 65 patients with "chronic arthritis" demonstrated to Martin [255] no variation which he viewed as abnormal, considering the patient's build, age, and abdominal muscle tone. Minor changes were frequently found by Holbrook,[193] major alterations rarely.

In considering the etiologic importance of intestinal disturbances one must distinguish between the bowel as a focus of infection and as a source of intoxication from abnormal food products. The latter may depend in part on the former, but it is the second idea that the adherents of the metabolic theory stress, believing that arthritic patients either eat foods which are poisonous to them because of idiosyncrasy, or partition their food unhealthily in the direction of an excess of one type of food, such as sweets and starches. Eaton [260, 261] surveyed the eating habits of 270 patients with atrophic arthritis, but found no discernible differences between their habits and those of nonarthritic persons. Their diets contained adequate amounts of protein, vitamins, calcium, and minerals, and there was no evidence of an imbalance in favor of either acid or alkali-forming foods. Alcohol or tobacco seemed to be of no significance. (Detailed food charts are given, but they were not summarized as to the relative amounts and type of carbohydrates used.—Ed.)

Noting a "tendency" to increased values of uric acid in blood and synovial fluid of patients with chronic arthritis, a "feeble attempt" on the part of such patients to adopt a low purine diet, and reports to the effect that uric acid metabolism may be related to allergy, Eaton considers "chronic arthritis" and allergic disease related to an unknown precipitating factor, excess uric acid serving as the predisposing factor. (The uric acid values recorded—the method was not stated—are by no means consistently high and one would agree with the author that the data are insufficient for final conclusions.) Martin also noted somewhat high values of blood uric acid in a number of cases of "chronic arthritis."

Abnormal sugar tolerance curves were noted in a high percentage of the cases by Martin and by Shackle and Copeman, [262] although fasting levels of blood sugar were essentially normal, as was also shown by Eaton and Cocheu.[219] The sugar content of both arterial and venous blood was determined by Shackle and Copeman. Had the difference between these two levels been less than the normal differences, they would have agreed with Pemberton that the cause of the rapid rise of the blood sugar in atrophic arthritis might be due to a failure of muscles and other tissues to utilize sugar, thus causing "unused sugar" to increase the amount in returning venous blood. In the majority of cases, however, normal or even greater differences were observed, similar to those seen not infrequently in true diabetes. In spite of clinical improvement, there was no marked improvement in subsequent tolerance curves.

Studies on Circulation and Skin Temperature. Opinions regarding the frequency and significance of circulatory alterations in arthritis are conflicting. It has been stated that patients with atrophic arthritis generally have a lowered skin temperature of the extremities, low blood pressure, and a reduction in size and number of surface (nail-bed) capillaries. It is assumed that a similar state of affairs occurs in joints, and that this is a potent factor in initiating and keeping up the disease. Kovacs, Wright,

and Duryee [263] studied 40 cases of atrophic arthritis and 40 of hypertrophic arthritis. A subnormal surface temperature was found in an equal number of the cases (in 52.5 and 50 per cent, respectively). A decrease in the number of capillaries was seen in 30 per cent of the cases of atrophic arthritis but not in cases of hypertrophic arthritis except in fingers with pronounced Heberden's nodes. Small constricted capillaries were seen in 53 per cent of the former, 28 per cent of the latter; a slow blood flow was present in 65 and 52 per cent and tortuosity in 35 and 60 per cent of these cases, respectively. There was a definite relationship between slow blood flow, lowered surface temperature, and increased sedimentation rate. However, none of the circulatory changes consistently paralleled the activity or extension of the arthritis, and because the changes were not consistently present they could not be considered of etiologic importance. Furthermore, it is not established that the condition of nail-fold capillaries is duplicated by articular capillaries. The skin of arthritics is slightly less responsive to histamine tests than normal skin, according to Bisset and Woodmansey [264] who also noted paucity of capillary loops but considerable attenuation, with long straight loops readily visible. Patients with atrophic arthritis show a lag in the return of color and temperature to extremities after the application of the Moskowicz test (the alternate application and removal of a tourniquet); Rich [195] believes this affords evidence of a diminished circulation. According to Bick,[265] patients with atrophic arthritis display hypotension and a frequent tendency toward a progressive narrowing of the dorsalis pedis artery, or at least a diminution of its pulse. Atrophy and discoloration of skin are early evidence of insufficient circulation which generally remains compensated. However, in the Montefiore Hospital, there are always several cases of end-stage rheumatoid arthritis in which vascular obliteration is so far advanced that one or even several extremities have become gangrenous as a result of vascular obliteration and an added neurotrophic factor. Biopsy of articular tissue and bone in cases of old inactive atrophic arthritis showed hypovascularity, with a decrease in size and number of smaller vessels and extensive atrophy of bone, probably due to decrease in vascular patency. (The editors recall but one somewhat similar case—a case of Osgood's in which there was extensive trophic changes of skin and nails but no definite gangrene. Since related gangrene in atrophic arthritis has not been reported, a finding that could hardly escape attention, one wonders whether unrelated vascular occlusion may not have been present in Bick's cases. More studies are desirable, particularly on the frequency and time of appearance of such circulatory changes in normal persons and chronic invalids of different ages. So far, no control studies have been presented by anyone. Not a few arthritic patients with severe but afebrile arthritis have warm, not cold, hands, as Drukker and van Breemen [266] have shown. Of 100 patients, 16 and 22 had always had cold hands and cold feet, respectively. Thirteen patients noted cold skin with the onset of their

arthritic pains. Twenty-four had blue hands after the disease started, but 23 still had warm hands and 10 had warm feet.—Ed.)

Treatment of Atrophic Arthritis

A program of treatment based on an acceptance of the infectious theory naturally differs in principle and in some particulars from one based on an adherence to the metabolic or endocrine theory. At the hands of thoughtful specialists, however, these differences are by no means as great as one might suppose, because the deficiencies of each theory are only too well recognized by them and the inadequacy of a program narrowed to fit some favored hypotheses is sometimes too painfully apparent. In one case the initial emphasis may be laid on removal of infected foci and on an attempt at bacterial immunization or desensitization. In another, first consideration may be given to the insurance of proper nutrition and intestinal elimination. In the last analysis, however, the considered therapeutic program of the majority of those of wide experience in the care of arthritis is essentially the same, not as different as one might infer from the publications of each where a favorite theme is, with entire propriety, emphasized. The skeptic or therapeutic nihilist may suggest that, faced with a progressive and resistant disease, the "infectious theorist," for example, will soon enough come to the end of his road and gladly try the schemes of another. It is not for this reason, however, that physicians are adopting a broader viewpoint and an inclusive plan of treatment, but because modern studies have shown how intricate is the disease called atrophic arthritis, and how imperative it is to approach it by every possible avenue. The statement is not borrowed without justification: "Know arthritis and one knows medicine." Testifying to the profession's enlarged outlook is the increasing recognition of the importance of studying the soil of the affected patient and not just the seeds of disease, of recognizing phenomena which subtly but often unmistakably announce the prologue to rheumatism. These prodromes have been reviewed: unaccustomed fatigue and chilliness, transient pains in muscles and joints, vague vasomotor and sensory disturbances, mild declines in appetite and weight (Painter,[267] M. Smith,[205] Minot[268]). It is often difficult to appraise such complaints. In the beginning one must certainly treat them with discretion and not be a prophet of impending doom. Once they are unmistakably and significantly present, a reasoned plan of attack is in order, first things first. Readily removable foci of infection should be cared for promptly. Gentle regulation of the daily habits of the patient is apropos—the establishment of a daily budget of rest and moderate nontraumatizing activity, of a balanced diet, and proper elimination. Painter rightfully insists that when adequate treatment is instituted in the prodromal and early stages of rheumatism, much permanent joint injury can be prevented; often the disease stops forthwith. Unfortunately no statistics are available concerning the thousands of persons with whom

arthritis has but flirted, to be driven away by gracious Nature, aided perhaps by an alert general practitioner. Were such data revealed, it would surely give encouragement and a more proper perspective to those who see the other thousands who procrastinated or were neglected until the disease was firmly established. No program of treatment is suitable for these patients en bloc. Treatment must be individualized to fit the person perhaps more than his disease. It will be conservative or radical as circumstances of the moment dictate. In appropriate cases, it may be altered frequently or remain essentially unchanged for weeks. With this foreword, a review of current methods and opinions of their worth are given.

Recognition and Management of Infected Foci. Ryerson [269] considers infected *tonsils* the commonest cause of atrophic arthritis. Foci "above the vocal cords" are probably primary, according to Burbank [224]; those below the cords are secondary. An unusual infection was considered by Fitzgibbon [270] to be a probable focus, for example, the esophagitis of a woman, aged 31, who developed a progressive polyarthritis after "pneumonia." Shortly thereafter, she had "pulmonary tuberculosis." Still suffering with arthritis in spite of removal of infected foci, she noted difficulty in swallowing. Dilatation for cardiospasm was followed, curiously, by "striking improvement" in both her general and joint condition. Three years later arthritis and cardiospasm recurred simultaneously. After another esophageal dilatation both cleared up. While pregnant, a year later, the cardiospasm but not the arthritis recurred. Shortly after pregnancy was completed, both the arthritis and cardiospasm again recurred and were once more relieved by esophageal dilatation.

A recent study of *sinus infection* in relation to arthritis has been made by Snyder, Fineman and Traeger,[271] and Hurd,[272, 273] who believe that sinusitis is as common and as important in arthritis as is tonsillitis. Many cases of "silent sinusitis" are missed. Sixty-eight per cent of 386 consecutive patients with atrophic or hypertrophic arthritis had "pathologic changes" in the sinuses; 74 per cent of the latter showed infection both clinically and roentgenologically and 17 per cent of them gave no history suggestive thereof. Fifty-four per cent of 43 patients whose sinusitis was untreated failed to show improvement in joints. Seventy-one per cent of 28 patients whose sinuses were treated conservatively and 89 per cent of 18 whose sinuses were operated on were "cured or showed marked improvement." Roentgenograms, transillumination, direct examination, and douching are all considered necessary to reveal the "silent" cases, some of which may be purulent.

A spray of an appropriate bacterial emulsion is recommended by Burbank for the "local vaccination" of chronic nasopharyngitis.

Although the *gall-bladder* is not a common focus, it is infected in about 3 to 5 per cent of cases of atrophic arthritis, according to Judd and Hench.[274] In some cases cholecystitis and infections of joints bear an indirect relationship, both probably arising from some other and primary focus. In other

cases, infections of the gall-bladder may serve as a focus for arthritis, as it may harbor organisms, generally streptococci, but occasionally staphylococci or bacilli, capable of producing experimental lesions in the joints and gall-bladders of animals. Bacteriologic and pathologic observations have been made in 55 cases of chronic infectious arthritis in which cholecystectomy for coëxistent diseases of the gall-bladder was performed. In several cases, gall-bladder tissue contained arthrotropic organisms. In five cases symptoms related to joints were completely relieved, in eleven cases there was marked improvement, and in eight there was definite, although moderate, relief following operation, a total of 52 per cent. The joints of the remaining 21 patients were not appreciably affected by cholecystectomy. Judd and Hench concluded that when definite surgical indications for cholecystectomy are present, it is justifiable to urge surgical intervention in the hope that the arthritis may be definitely benefited. Further experience is necessary before one can urge removal of the gall-bladder for arthritis when the indications for operation, aside from the arthritis, are not definite. A conservative attitude is probably desirable, yet the nature of chronic infectious arthritis is so malicious that a radical attitude in individual instances may be justified, provided surgery is advocated and accepted without unwarranted promise of benefit.

According to Hartung and Steinbrocker [275] the incidence of gall-bladder disease in chronic arthritis is 4.5 per cent (nine of 200 consecutive cases of arthritis; three cases with infectious arthritis and six with osteo-arthritis). This was an incidence no higher than that in any general hospital's admissions. Of the 200 arthritic patients, 30 were suspected of having cholecystitis or stones by history or physical examination, but in 25 cases cholecystograms were negative. By microscopic and bacteriologic examination of the material obtained by duodenal drainage, four of these radiographically normal gall-bladders were found to be affected. On the basis of these statistics, and from the fact that no relief to joints was provided by cholecystectomy and duodenal drainage in one case, it was concluded that cholecystitis is apparently not an etiologic factor. (The tropism of organisms isolated by drainage or at operation was not determined by the latter workers. The failure of treatment in one case is insufficient to permit conclusions on the results of otherwise indicated cholecystectomy in arthritis. —Ed.)

The possibility of the *bowel* being a focus for arthritis remains a vexing question. This problem is aside from that concerning the likelihood of its containing food toxins. Space forbids that we discuss auto-intoxication in extenso here. Many believe that arthritis originates from intestinal bacteria (Smith [276] and Traut [242]). Traut and Herold [277] found streptococci (viridans and hemolytic) more commonly on the rectal mucosa of arthritic patients than on those of controls, but the number found bears no relationship to the severity of the disease. Fifty-three of 60 arthritic patients showed such germs (but only three of 15 controls). The patients'

serums contained strong agglutinins thereto. Exacerbations and remissions of joints were related to variations in "gastrointestinal dysfunction." The germs, when injected intravenously into rabbits, did not produce arthritis but did so occasionally when injected into the colon.

Infections of the genito-urinary tract (prostatitis and vesiculitis) were the only foci found by Hayes [278] in 40 per cent of 50 cases of arthritis. In many more such infection was found in association with infected teeth or tonsils. When conservative treatment fails to afford relief in the face of progressive arthritis, radical measures, even vesiculectomy, may be justified. When *endocervicitis* is present, pelvic diathermy and ionization may be helpful (Robinson [279]).

Time for Removal of Foci. The optimal time for, and the dangers incident to, removal of foci have long been the concern of many. "Cruel as arthritis is, few of its victims lose their senses." That that is left for their physician to do is the inference one gains on reading the critique of one (Mayers [280]) who, while granting a meed of praise to focal removal, insists that patients have been made temporarily worse or even permanently crippled by the removal of infected teeth at the wrong time. Gruesome "before and after" pictures are shown: one of a young man "before removal of a tooth" and "two days later—permanently blind"; one of a boy "before alveolectomy" and the same patient later "dying of endocarditis which appeared four days after removal of a tooth"; three others who suffered "rapid destruction of eyes after tooth extractions." The appearance of such reactions may be prompt or delayed. "The fuse the dentist has lighted is a long one and the explosion may not take place for a week, a month or even several months." Adequate preparation and technic will tend to minimize or prevent such catastrophes.

(The editors lay claim to not a little experience in the field of focal removal for arthritis but confess that significant exacerbations after removal of foci, long heard of and much looked for, have very rarely, and in the case of most of us never, materialized. Reports such as these generally give no statistics on the number of removals followed by no reaction, or on the normal expectancy of minor and major flare-ups in the course of arthritis without focal removal. Until such data are at hand, based on our own experience, we feel that the bugaboo of a significant postoperative flare-up is considerably overemphasized. That some, without painting so dire a picture as the one above, do not entirely agree with us is however evident from the following.—Ed.) "The early removal of foci is indicated but the patient should be built up before undertaking debilitating surgical procedures" (Minot [268]). "In the beginning it is more important to destroy the infection than to remove foci. Extraction of teeth may admit streptococci into the blood stream. After the infection has disappeared either spontaneously or as a result of treatment consideration of possible foci may then be investigated" (Miller [281]). "Focal removal should be performed only when the patient's general condition has been improved with

the aid of autogenous vaccines" (Anderson [234]). "Foci in some cases should at first be left alone, to be dealt with after the general condition has been greatly improved" (Crowe [282]). "In some of the more febrile cases a real hazard exists in removal of foci, which are not removed during or near an acute phase of the disease, and before the removal of which a transfusion is occasionally given" (Holbrook [193]). (In the face of a progressive arthritis, when the "building up processes" do not otherwise materialize, procrastination in removal of foci certainly seems unwarranted, and the risk thereof is justified if foci are removed in conformity with good clinical and surgical judgment.—Ed.)

The removal of foci in patients whose arthritis is many months or years ("five years or more"; Holbrook [193]) old is rarely if ever followed by improvement in joints. Their removal early may be of great value. The effects were noted by Miltner and Kulowski [283] in 100 cases of atrophic arthritis. Of 37 patients less than 16 years of age, 73 per cent were "apparently cured" and 16 per cent "markedly improved." Of 63 patients more than 16 years of age, only 15 per cent were "cured," but 58 per cent were markedly improved. Of 100 patients with hypertrophic arthritis, none were cured and 91 per cent received no improvement from removal of foci. According to Stainsby and Nicholls,[284] removal of foci is more likely to help than vaccines. Fifty-eight per cent of 103 patients with atrophic arthritis were "improved" after tonsillectomy. Sixty-nine per cent of 35 patients were improved after the removal of abscessed teeth. Vaccines helped only 36 per cent. Complete and permanent cure following removal of foci was exceedingly rare, but a rather high percentage were "favorably affected." Some foci probably responsible for arthritis are permitted to remain because criteria for the estimation of infection therein are often too rigid.

Others are disappointed by removal of foci. In Holbrook's cases of nonfebrile atrophic arthritis, no one patient was unquestionably benefited thereby. In his other group ("atrophic arthritis with evidences of infection," fever, malaise, red or hot joints), early removal of foci many times abruptly halted the disease.

Dietotherapy. Diets are given in arthritis to reduce or to eliminate a supposed auto-intoxication (food), to reduce a presumably etiologic intestinal infection, to correct a supposed deficiency in minerals or vitamins, to remove the irritating trauma of obesity or to increase the patient's "nonspecific resistance" (Hench [285]). It is obvious that there is no one "diet for arthritis"; it depends more on the patient than the disease for which diet is given (Minot [286]).

Since most of his patients had digestive disturbances (intolerance to starch), Traut [227] reduced the starch content of their diets with reported improvement. Pemberton's diet (low in carbohydrate, low in calories) is approved by Bethea,[287] and by Meader [241] who sees no warrant for withholding meat or "acid" fruits unless a definite idiosyncrasy is proved. Pemberton's diet was associated with no significant improvement in the

cases of Wetherby,[200] and of Seybold.[288] Fletcher's diet, in which emphasis is placed on vitamins (with a low carbohydrate intake advised chiefly to enhance the utilization of vitamins), was approved by Buckley[289] and by Holbrook.[193] According to Brown,[290] the food factor in arthritis has been overestimated, and many patients suffer from over-dieting. Physicians, misled by false analogies to gout, too often restrict meats, an adequate supply of which is vital to combat anemia, fatigue, and loss of weight. Restriction of proteins often does more harm than good, according to Fletcher,[256] who finds no chemical support for the use of alkaline diets and is rarely able to demonstrate definite food idiosyncrasy or allergy.

The use of small doses of *insulin* (generally with a high-calorie diet) is recommended as a "fillip" for weak, anemic, underweight arthritic patients with anorexia or loss of appetite by Shackle and Copeman,[262] Ellman,[291] Eaton,[261] and Fletcher.[256] Ellman uses five units daily for one week, injections being given 20 minutes before the principal meal and followed by glucose or milk to avoid hypoglycemia. The insulin is increased weekly by five units until 30 units (15 units, twice daily) are given. When all other measures fail, appetites can thus be stimulated. Eaton used 5 to 30 units (twice daily) in conjunction with a high-caloric diet.

Additional Intestinal Therapy. Supposed intestinal antiseptics are still being recommended: acidophilus milk (Smith[276]), colonic irrigations (Miltner and Kulowski,[283] Ellman,[291] Burbank[224]), mineral oil, and mild cathartics or preferably oil retention enemas (Holbrook). Burbank treats the gastrointestinal tract by the use of a bland, low carbohydrate diet and daily capsules of saponified heart tissue lipin. Ryerson[269] utilizes a two week "laxative test" as an indication for intestinal therapy, but he fails to say what should be done thereafter if joint pains are reduced. At times Smith relieves ileocecal stasis surgically.

Vaccines. Come depression or prosperity it's a poor season indeed that doesn't present its "vaccine of the year" for atrophic arthritis. Since the popularity of each lasts a span of years, at any given time there are several "favorites" extant. Some of them in current favor are those of Burbank, Cecil, Clawson and Wetherby, Crowe, Rosenow and Small. In addition numerous physicians "go on their own" to make and use personal vaccines from autogenous strains.

Cecil favors a three to four months' trial of vaccine, using his typical strain. All symptomatic reactions are avoided. Better results were obtained for private than for dispensary patients, and by the intravenous rather than the subcutaneous route. His colleagues, Stainsby and Nicholls,[284] obtained "improvement" in 36 per cent of 194 patients treated with vaccine alone. The results were essentially similar regardless of the type of vaccine (autogenous or stock) used and regardless of the method of administration (subcutaneous or intravenous).

On the basis of animal experiments in which agglutinins were augmented by the intravenous more than by the subcutaneous route, and from

which evidence was obtained suggesting that subcutaneous vaccines tend to increase rather than to decrease the hypersensitive state, Clawson and Wetherby [199, 200] treated 365 patients with "chronic arthritis" (undifferentiated) by the intravenous route, using their favorite "rheumatic fever strain." Eighty per cent had clinical improvement manifested, in most cases after 10 injections in five weeks. Improvement as a rule did not occur until the agglutinating titer of the patient's blood rose to 1:6400 or more, and foci of infection were not removed until such a concentration of agglutinins had been obtained thereby.

Autogenous and complement-fixing strains, mainly of streptococci, are used by Burbank [224] in doses small enough to avoid reactions. The complementary titer of the patient's blood is, he believes, an index to the value of vaccine. Burbank's vaccine or autogenous vaccines, prepared after the method of Burbank, are used by Anderson,[234] by McBride [292] and by Ryerson [269] with "marked improvement in many cases." Patients with both atrophic and hypertrophic arthritis were treated by Burbank and Ryerson. Some of them, especially those with hypertrophic arthritis, were not benefited in any way. So far as Ryerson could see these vaccines harmed no one. Burbank's method of preparing vaccines includes killing the organism by phenol rather than by heat, a method which Hoover feels makes them more specific. Hoover [293] obtained "good results" with a large majority of those willing to accept "a rather long period of treatment" (no statistics given). Most of these workers rely on measures other than vaccine alone.

Crowe believes that atrophic arthritis is primarily due to *Staphylococcus albus*, with streptococci as important but secondary invaders, that hypertrophic arthritis is due primarily to streptococci, secondarily to *Staphylococcus albus*. (This makes vaccine therapy convenient indeed.) Eight hundred and two patients have been treated with weekly injections of Crowe's stock vaccines alone. Crowe and Young,[294] in their second report (first report Lancet, 1930), analyzed results in 65 cases of atrophic arthritis, 245 of hypertrophic arthritis, 218 of "mixed types," 217 of fibrositis, 38 of neuritis, and 21 of "other types." Results in the atrophic, mixed, and hypertrophic group, respectively, were: symptom free 17, 6, and 8 per cent; much improved, 35, 40, and 32 per cent; improved, 32, 42, and 46 per cent, and not benefited, 16, 12, and 14 per cent. "Striking improvement" generally occurs between the tenth and fifteenth week of treatment. The size of doses depends on the patient's reactions. In one case the same dose (the smallest dose that gives relief without reaction) may be used for months. A fifth of the patients tend to have a relapse in spite of continued treatment. More than 40 per cent go on to further improvement. (The authors admit that no controls were available. While results were based in part on examinations, they were apparently graded largely by the patients' answers. —Ed.)

Crowe's vaccine alone was used by Thomson [295] in the treatment in 106 cases: 25 atrophic, 44 hypertrophic, 12 "mixed," and 25 fibrositis. Re-

sults are not analyzed for separate groups. Of the patients, 25 per cent were "completely relieved" of symptoms, 65 per cent were considerably relieved, and 10 per cent had little or no relief. (These results are after one to 10 months of treatment, a time entirely too short for a thorough appraisal. No controls are given.—Ed.)

Autogenous vaccines, made from various strains of streptococci from different sources (blood, synovia, feces, foci, lymph nodes) and given by different routes and in differing doses (initial dose from 15 or 20 (Rawls, Gruskin and Ressa [204]) germs to 100,000 germs) are preferred by many (Goldfain,[296] Cadham,[239] Lautman,[236] Ashworth,[225] Gray, Fendrick, and Gowen,[107, 108] Vaughan,[240] Traut,[242] Miller,[297] Meader,[241] Buckley [289]). In some instances only those strains were used to which the patient was skin-sensitive. Small doses were favored with the idea that desensitization, not immunization was being accomplished. In 48 cases 81 per cent of patients were improved by intravenous vaccines of various streptococci isolated from throat cultures by Rawls, Gruskin, and Ressa.[204] Specificity was presumed if agglutinative titers were greater than 1:160. Cadham noted "some amelioration" in 80 per cent and "complete relief" in many, of 90 cases of "chronic polyarthritis" in which he used autogenous strains presumably of the peculiar pleomorphic organisms isolated by him from regional lymph nodes. Vaccines made from germs isolated from feces were used by Vaughan (47 per cent of 100 patients with "chronic arthritis" improved satisfactorily) and by Traut.[242] Forty-eight per cent of 27 patients with "chronic arthritis" treated by Traut without vaccine recovered or were greatly relieved. Thirty-one patients unrelieved by other measures were treated by vaccine: 68 per cent were markedly or completely relieved. Agglutinins to these strains were present in high titer in patients' serums before therapy was instituted.

Speaking of "fecal vaccines" for arthritis, Brown [290] says, "I never subscribed to the view that if you couldn't find a septic focus anywhere you could at least give vaccines prepared from intestinal flora. I always felt that it was a poor bowel that couldn't give something."

In contradiction to the adherents of vaccine therapy, many are "disappointed" in vaccines, and use them skeptically or not at all. According to Miller [133] "their value is still open to question." Minot regards them as "of doubtful value," possibly harmful if reactions are produced. To Ellman [291] they are "unsatisfactory." Kinsella's [298] experience with streptococcal vaccines and extracts was "not encouraging."

Congdon [299] treated 331 patients with "infective arthritis" either with autogenous or stock vaccines, the latter prepared from 40 strains of *Streptococcus viridans* isolated from infected foci. A smaller number of controls were observed. Congdon concluded that such vaccines do not hold out any better prospect of improvement or cure than other current methods.

Of 103 patients treated by Stainsby and Nicholls,[284] 20 had tonsillectomy alone, 83 had tonsillectomy and streptococcal vaccine intravenously or sub-

cutaneously. Improvement was no greater for the latter than for the former. An estimation of the value of vaccine must consider its psychological effect and the fact that some patients will improve anyway.

In the treatment in 100 cases Holbrook [193] used almost every combination of antigen and method of administration for nearly every degree of atrophic arthritis. Repeated skin and agglutination tests and clinical criteria were used in evaluating results. He concluded: "undoubted clinical improvement, not easily accounted for otherwise, occurred only occasionally. No single one of the above groups did well enough to show clearly superiority of results over other groups not receiving vaccine. Our best results with vaccines have occurred where an autogenous organism which showed a strong positive skin sensitivity test, was used in small desensitizing doses intravenously. We have had a few dramatic results in this group of patients." Dawson and Boots [213] treated several hundred patients with atrophic arthritis, using small and large doses of autogenous vaccines subcutaneously and streptococcal "antigens," typhoid vaccine, and hemolytic streptococcal vaccine subcutaneously and intravenously. As controls, some were given weekly injections of minute amounts of isotonic sodium citrate. They concluded that their value remains unproved. It was found impossible to influence favorably the sedimentation rate in general. Those treated otherwise than with vaccines were equally improved.

Pemberton [253] regards vaccines as a definite arm of medical therapy: "However, (he says) in many arthritic clinics vaccines are rarely required. In Philadelphia we have to hunt to find cases in which they are really needed. I have difficulty in getting such cases to show to postgraduate students."

To appraise the value of vaccines, Miller [281] obtained the opinions of a number of internists, immunologists and bacteriologists. His conclusions were as follows: (1) The not infrequent, brilliant therapeutic results which seem clinically to follow vaccine administration justify the belief that vaccines do have a rôle in the comprehensive treatment of the arthritic patient. The specific indications for the use of vaccines, their optimal dosage or method of administration, etc., are still open questions. At the moment it would appear that vaccine therapy in chronic arthritis is appropriately limited to the atrophic form, and has little, if any, application in the hypertrophic type. (2) The consensus of opinion inclines to the view that the mechanism whereby improvement occurs under vaccine administration is in some way related to a desensitization process rather than to the formation of specific antibodies. In harmony with such a conception, small doses of vaccine are most advocated, given preferably intravenously, and continued over a long period of time, avoiding pronounced constitutional reactions. (3) Regardless of whether this conception is substantiated or not, it would seem apparent that in the light of more recent bacteriologic studies, greater attention should be paid to the process of vaccine preparation, chiefly in terms of attempting to secure virulent strains of the autogenous disease-provoking organisms and the avoidance of such measures as promote antigenic dissociation in

preparing the vaccine for therapeutic use. (4) At present there are no so-called immunologic or laboratory procedures which are established standards or indexes of the therapeutic value of vaccines in the comprehensive program necessary for any arthritic patient. Finally, it is to be hoped that more rigorous regard for some of these principles which have been briefly alluded to, will, for the time being, both retard the extravagant claims which are made by some as to the value of vaccines in chronic arthritis, and at the same time provoke a more serious consideration of the definite purpose for which vaccines are used.

(As do others, the editors of this review differ on the value of vaccines. Two favor their use; two use them only occasionally; two do not use them at all. All are agreed however that a trial of vaccine therapy is entirely justified for a patient whose painful arthritis is "standing still" or getting progressively worse, uncontrolled by measures used. In such cases reactions should be avoided, the patient should not be promised too much but be told that it may or may not help, and the cost of vaccine administration should be light; under no circumstances should it be a burden.—Ed.)

Antistreptococcal serum seems to be rarely used. Goering [300] reported beneficial results in one case.

Foreign Protein Therapy. Similar differences of opinion exist as to the value of foreign protein therapy. It has the approval of Miller,[133] Dill,[301] Goering [300] and Hench.[302] Murray-Lyon [303] treated 28 patients with foreign proteins intravenously, 16 with peptone, 12 with typhoid vaccine. They all showed a greater immediate response to treatment than did 12 control patients but at the end of one to five years the results for the two groups were very similar. Meader [241] and Ryerson [269] noted temporary improvement only, and Meader feels that the danger of serious exacerbation and of irreparable injury is too great to warrant its use.

To determine the type and incidence of such dangers, Hench [302] reviewed his experience with the administration of about 10,000 injections of typhoid vaccine intravenously to 1,500 patients with atrophic arthritis and to 1,000 with other diseases. He also made a complete survey of the literature in search for reports of unusual and untoward reactions. The reactions were in general well-borne, and Hench concluded that the beneficial results from protein therapy justify its continued use and further development. Unusual reactions to such treatment have been rare at The Mayo Clinic; they occurred in 14 cases in all, an incidence of about 0.5 per cent. They occurred 16 times in the treatment of 11 patients with atrophic arthritis, once in a case of rheumatic fever and three times in the treatment of two patients with occlusive vascular disease. Thus, of 10,000 injections, only 20 were followed by an unusual reaction, an incidence of 0.2 per cent.

The mechanism of both the usual and unusual reactions is fully discussed. Unusual reactions result from the stimulation of inflammatory foci of either infectious or noninfectious origin, stimulation of latent diathetic phenomena, and from some marked vasomotor or intravascular

chemical change that may produce acute thrombosis or vasomotor imbalance. Thus the unusual reactions occurring subsequent to injection were: acute and subacute appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, vascular thrombosis, and renal insufficiency. Death occurred in three instances, a mortality of 0.12 per cent (about 1 in 1,000 patients). This constitutes a very small risk but a risk that must be recognized and that can probably be avoided by more careful selection of patients, using it with special caution for patients over 50 years of age and not at all for patients markedly exhausted or debilitated. Except in certain conditions, of which pulmonary tuberculosis is one, the known presence of latent or quiescent foci should not act as a contraindication to foreign protein therapy. Indeed, part of the value of such treatment lies in the possible demonstration of suspected or unsuspected foci otherwise undemonstrable at the time. Such reactions, if their significance is appreciated, may be advantageous rather than detrimental. The recognition that such reactions may very occasionally occur, will lead to a more judicious use of such treatment, but the compilation of reported reactions should not give them undue emphasis to the detriment of a useful and essentially safe form of treatment.

Transfusions. A series of small blood transfusions has been advocated by Copeman.[304] Holbrook treated 70 patients in this manner and found that in the subacute and early phases of "infectious arthritis" with or without anemia, they responded well and in not a few instances dramatically. The temperature may drop to normal, the pulse be slowed, joint effusions disappear, and the patient gradually recover. Transfusions were of little help for chronic afebrile patients with advanced bony changes. Transfusions of 300 c.c. of blood weekly, for debilitated patients, are advocated by Buie.[190]

Various Medicinal Preparations. The debatable value of various antirheumatics has been recently reviewed, Hanzlik (1929), Young (1930), and Mutch (1931). Bethea [287] cites the use of 88 "anti-rheumatic" drugs, ascribing worth to only a few. Dill [301] and Kauffman [305] describe the rectal administration of salicylates to patients who have a systemic aversion to their oral use. Ascending doses of 50 to 250 grains of sodium salicylate are given, twice a day, by rectal injection or drip with four to six ounces of water or in two ounces of a watery cornstarch solution (12 ounces of water previously boiled with 2 drachms of cornstarch). The supposed advantage is that "mammoth doses can be taken without gastric upset." (Hanzlik's comment on rectal administration of salicylates is recalled: there is little or no reaction because absorption is poor. When the patient actually absorbs therapeutic doses he cannot avoid salicylism.—Ed.)

The prolonged or careless use of cinchophen is felt to be dangerous by Dill.[301] Oxyliodide seems of little value to Meader.[241] The toxic effects of amidoxyl benzoate (ammonium orthoiodoxybenzoic acid) have been reviewed by Bell and Richmond,[306] who report an instance of fatal poisoning thereby. Cod liver oil (1 to 2 drachms, three times a day), viosterol (10

to 15 minims daily), or halibut oil with viosterol (10 to 15 minims daily) are approved (Dill and others). Hypochromic anemia will be helped by iron only if the disease is relatively inactive (Minot [286]). Arsenic and sodium cacodylate are still used by some (Buie,[190] Seybold,[288] Minot, Dill).

Thyroid gland therapy was of real benefit to only 17 per cent of 103 patients treated by Hall and Munroe.[254] For patients whose history suggests "deficient ovarian secretion" Haggart [307] uses amniotin pessaries in conjunction with thyroid extract. Endocrine therapy may at times bring about improvement, but according to Brown,[290] will rarely completely cure any joint disease.

Sodium aurothiopropanol sulphonate (allochrysine) was given intramuscularly in a series of injections to 44 patients by Forestier.[207] Seventy per cent received a "good" or "very good" result. A few toxic reactions were seen: stomatitis in 20 per cent, skin reactions occasionally. Renal insufficiency is a contraindication to treatment.

Octozone (O_8), a new form of concentrated ozone, has been advocated by Parkes [308] for its oxidizing effect. It is produced by passing oxygen at a pressure of five atmospheres in an "electroniser." It can be administered by mouth, as a skin bath, or by rectal or intramuscular injections.

The administration of chaulmoogra oil, after the method of McIlhenny (1931), was used by Hebert [309] in 21 cases. All but four patients were improved. Six to twenty injections of 3 to 5 c.c. were given into the gluteal region. Its oral administration seemed ineffective.

A revival of sulphur therapy is current, colloidal sulphur being the favored preparation. According to Cawadias (1925), patients with atrophic arthritis exhibit a deficient thiopexy, their cells have lost the ability to retain sulphur. As a preliminary to its use in arthritis, Wheeldon and Main [310] reported on the toxicologic effects of a colloidal sulphur preparation given by intraperitoneal or intravenous injections to rabbits. In clinical doses no apparent harm was observed. (A few 1934 reports will be analyzed in our next review.—Ed.)

Colloidal calcium and certain dietary recommendations are prescribed by Aulde,[311] who believes that the basis of arthritis lies in a chemical deviation involving calcium and magnesium.

The intra-articular injection of Pregl's solution is suggested by Thomson.[65]

Rest, Activity, and Physical Therapy. The value of physical therapy and the principles of its application are being increasingly recognized, but are worthy of constant restatement (Coulter,[312] Ray,[313] Buckley,[289, 314] Kovacs [315]). Rest is looked upon as the most potent single therapeutic procedure at our command, but rest does not necessarily mean bed rest. The latter, improperly carried out, may nullify its purposes (Minot). The arthritic patient who must be put to bed or kept physically quiet must not be allowed to remain wholly inactive or increased muscle atrophy, flexions, and other deformities may result (Pern [316, 317] and Munk [318]). A

judicious balance must be made, therefore, between mental and general bodily rest and rest for inflamed joints and muscles on the one hand, and nontraumatizing physical activity on the other. For an acute exacerbation, Anderson [234] feels that a maximum of a week or two in bed is generally sufficient; more may be dangerous.

While the more common types of physical therapy, such as dry heat, diathermy, massage, and exercises, are of great value, the pool bath in which patients may use muscles and joints in the water is of special value and should be more available (Ray,[313] Lautman [319]). The "glove bath," a variation in the application of heat for painful hands and feet, is described by Ray.[320] The hands, enclosed in rubber gloves or the feet in rubber socks, are immersed in hot water at a temperature of from 105 to 110° F. for 20 to 30 minutes daily. Buckley [28, 289] advises cold baths for robust patients, warm baths followed by brief cold effusions for less robust patients. Prolonged and habitual hot baths lessen the skin's diminished power to react promptly to its environment. The merits of various types of physical therapy are presented: Pistany mud (Schmidt [321]), infra-red rays, roentgen-ray treatments, and "fever therapy" (Dausset and Lucy [322]).

Roentgen-Ray Treatments. The beneficial effects of roentgentherapy in arthritis may, Langer [323] feels, result from its influence on the vegetative nervous system, disturbances of which are so frequently present. Roentgen-rays first irritate, later quiet this system. He treated 65 patients with atrophic arthritis, 138 with hypertrophic arthritis, and 160 with "mixed types of arthritis." Seventy-five per cent of his patients experienced increased pain for about 48 hours. In 28 per cent this increase of pain was prolonged for one to two weeks and was associated with general malaise. The majority of patients are benefited, although results may not be apparent in some cases for several months. Of 86 patients with marked vegetative nervous system disturbances, 63 were treated only over the corresponding ganglia and nerves; others received both local and articular paravertebral roentgen-ray treatment. The latter plan is preferred, but many of the former group were made so comfortable that local treatment over affected joints was omitted. Coldness and clamminess of extremities, and swelling and pain were diminished. A control series (number not given) treated by other means than roentgen-rays were not so benefited. Sixty per cent of 180 patients with atrophic arthritis treated by Kahlmeter [22] obtained marked relief. Scott [324] believes that hypertrophic arthritis and "infective arthritis" are uniformly benefited, but that atrophic arthritis is not. In this Hernaman-Johnson [325] agrees. Douthwaite,[326] however, noted benefit from roentgen-ray treatments in cases of spondylitis with extensive ossification of spinous ligaments.

Fever Therapy. In the light of subsequent events it has become the fashion to consider that foreign protein therapy, such as typhoid vaccine intravenously, was the first modern form of fever therapy, although it is not at all certain that fever was responsible for its benefits. Fever therapy is

the "newest" form of physical therapy. Following malaria treatment, fever has been induced by "super-diathermy," radiothermy, hot air-conditioned cabinets, and hot baths. Markson and Osborne [327] in 1933, and also in 1931, induced by diathermy a temperature of 103 to 104° F. for seven to eight hours in the treatment of "chronic infectious arthritis." One fever session a week was given for eight weeks. In six cases, two patients were "markedly improved," three were "improved," and one was not improved. "Striking results" were obtained by King [328] in an unstated number of cases of both atrophic and hypertrophic arthritis. Relief of pain and increased mobility were noted by all. In some cases a "cure" was simulated. Other patients were only moderately and temporarily benefited. Even "after complete relief has been attained," further fever sessions every few days are advocated by him to prevent recurrences. Speed [329] noted some marked improvements although at times relapses occurred (no figures given).

Carpenter and Warren [330] believe that arthritic patients respond better to fever provoked by diathermy than by radiothermy. Using diathermy, Bishop, Horton, and Warren [67] gave 26 treatments to 15 patients with chronic infectious arthritis. Two fever sessions of five hours each were given. Results were "very encouraging" in 63 cases of atrophic or hypertrophic arthritis treated with radiothermy by Tenney.[68] At the end of eight months, seven patients were symptom-free, 48 were definitely improved, 8 were unimproved. Pope [331] favors the use of hot baths or diathermy, and noted that at first "arthritics have their pains and stiffness greatly increased." Coulter [312] favors diathermy hyperpyrexia but uses hot baths to lower the cost of treatments. Berris,[70] using heated cabinets, treated 11 patients with atrophic arthritis with three sessions a week for three weeks. Three patients obtained "complete relief," and the majority were "definitely improved." About 60 patients with atrophic arthritis seen by Simpson, Kislig, and Sittler [71, 332] were each given two fever sessions at 104 to 105° F. for four to five hours by radiothermy and heated cabinets. Thirty per cent believed they had experienced a complete remission, an additional 30 per cent were "satisfied with the result." Forty-three patients were treated by Kohn and Warren.[333] Only one or two fever sessions were given to each. Benefit was obtained by 35 patients; pain rapidly diminished and mobility of joints increased. Eight were able to earn a living. Relapses within one to two years occurred with three patients who were relieved by further treatment.

Favoring diathermy electropyrexia, Markson and Osborne [327] reported further results in the treatment of 19 patients. They insisted that eight treatments at a temperature of over 104° F. for eight to ten hours, are required. Of the 10 patients so treated, seven (70 per cent) were benefited; complete relief was noted by one patient for 15 months, one for 21 months, two for 20 months; three were "improved" for 12 to 14 months (end of observation period). Of nine patients treated with shorter sessions (four hours), 56 per cent were improved; five were definitely improved for

three months or longer; three were improved for only one month. In a small series of cases (numbers omitted) Kovacs [315] noted failures and encouraging results equally divided. Patients with atrophic arthritis do not stand as high temperatures (not over 104.5° F.) as comfortably as those with gonorrheal arthritis. Auclair [334] noted complete failure in only seven of 80 cases of various types of "rheumatism" (no details given).

Cecil's [217] results "have been rather disappointing," and he believes the wave of enthusiasm for hyperthermia in arthritis is not justified. In a limited series (number not stated), no benefit was noted by some, only temporary effects in others; in a few cases improvement was apparently permanent. Kinsella [298] noted only temporary relief in an unstated number of cases.

Physiologic effects from fever therapy by various means seem to be about the same. The pulse rate rises to 130 to 150. Blood pressure rises, then falls. The electrocardiogram shows contractions of lowered voltage (reduction of amplitude). The leukocyte count may show an initial drop within two hours, and may then rise to 15,000. There is no change or, due to dehydration and concentration, only a slight rise in blood urea, uric acid, sugar, creatinin, and calcium. There is a loss of carbon dioxide with a tendency to a slight alkalosis and an increase in the pH of blood. The most noticeable alteration is that discovered by Simpson and his colleagues: marked loss of chlorides from blood and tissues. Patients lose from 20 to 26 gm. of sodium chloride with each session; there is no free hydrochloric acid in the stomach and the blood chlorides fall 40 to 100 mg. Simpson feels that chloride loss in sweat is responsible for symptoms of exhaustion, fatigue, nausea, vomiting, abdominal cramps, and muscular twitching, occurring during and after fever sessions, and that they are all practically eliminated by supplying by mouth large quantities (four to six liters) of chloride-containing fluids, such as iced 0.6 per cent saline solution.

In conclusion, reports to date have in general concerned themselves with small numbers of cases, observed at most for about one to two years. The number of sessions advocated has varied from one or two, to eight, or as high as 20, sessions being given from one to three times a week. Whereas diathermy and radiothermy were the original methods of choice, there has been a reaction in favor of simpler and less expensive methods, such as heated air-conditioned cabinets. Results have been variable: "disappointing" to some, with "87 per cent improvement" and not infrequent "cures" reported by others.

Climate and Clothing. Arthritic patients tend to wear heavy underwear and extra clothing in an effort to "keep out" the weather and to protect themselves against thermal and climatic changes to which they do not adapt themselves readily. Light, porous and loose-fitting clothing is preferable (Brown [290] and Buckley [314]). Changes in external temperature normally induce a rapid and effective vasomotor response in vessels of the skin. In the arthritic patient, such responses are laggard and incomplete. Flannel and

nonporous clothing tends to induce a sodden condition of the skin and further failure of cutaneous responses. In consequence, the patient feels cold and proceeds to cover himself with yet more flannel, aggravating the condition.

The explanation for the resulting " cold sweat " is given by Brown.[290] Sweat glands and blood vessels of skin are both under control of the sympathetics. Normally the sympathetic actions on these two structures are in an " inverse direction "; stimulation of sympathetics constricts blood vessels but causes sweat glands to secrete. Normally, as sweating occurs with flushed skin vessels, one set of sympathetic fibers is thrown into action and the other set of fibers is inhibited. If both sets are stimulated simultaneously, the " cold sweat " of disease or emotion results.

Clothes which are very porous, with a network enclosing air, are both warmer in winter and cooler in summer because they permit a more adequate cutaneous response.

It is difficult to determine the value of climate in relieving arthritis, as a change in climate is generally associated with the institution of other factors, such as rest and intensive physiotherapy. While no proof is offered by Holbrook [193] as to the specific rôle played by climate, he noted definite and sustained improvement in many cases of arthritis of the " last resorter type " and dramatic response in others in which treatment was not given by removal of foci, medicines, or vaccines. (Some patients, however, obtained no significant relief, and Holbrook has made it clear here and elsewhere that " climate is not a panacea for all chronic arthritis " and that, " without an adequate program of treatment chronic arthritis may continue as a crippling disease even in the Arizona desert."—Ed.)

According to Buckley [314] there is no inherent difference between seaside and inland climate in arthritis, but some seaside places appear to be more unfavorable for both arthritis and fibrositis because of climatic peculiarities not yet identified. Sunshine, per se, has no directly beneficial influence on arthritis, although in moderation it is stimulating to metabolism. Hot climates, and all humid and relaxing climates, are unfavorable to arthritis, and the prevalence of high winds is prejudicial. Buckley feels that arthritic subjects are usually better in cool climates and weather provided they are protected against undue exposure and dampness.

Climate may play a more obvious rôle in the prevention than it does in the cure of arthritis. Since it affects Indians of Montana, Wyoming, and Dakota, but apparently has not affected any of a tribe of 5,000 Indians of the Tucson Desert, Holbrook believes the advantage of Arizona's climate is established. Factors of diet, foci, and so forth, were considered: there seemed to be only one variable factor—the climate. Of 1,000 consecutive cases among whites seen by Holbrook, in only one case was the patient a resident of Tucson. Only two local cases were found in the practice of 122 physicians in that locality.

Synovectomy. Reduction of pain, and considerable restoration, some-

times complete, of function may follow synovectomy, according to Painter [335] and Bernstein [336] who thus treated 4 and 25 patients, respectively. Painter operated in relatively inactive cases, removing the product of previous inflammation which was putting the joints at a mechanical disadvantage by distending the capsule, thus rendering the joint unstable. Bernstein got poor results in cases of multiple atrophic arthritis with lesions of cartilage, but when the latter were not present the results were good.

Sympathectomy. Sympathetic ganglionectomy and ramisectomy was proposed by Rowntree and Adson (1927) for the treatment of arthritis. Favorable results in selected cases were reported by them and others. It has been suggested by some that the operation provided only a temporary increased blood flow to involved regions. Thus Johnson, Scupham, and Gilbert,[337] making plethysmographic studies in a case of atrophic arthritis before and after unilateral cervical sympathetic ganglionectomy and ramisectomy, noted an early relaxation of blood vessels, but a recovery of independent tone of vessels 21 days after operation. No permanent increase of peripheral circulation was demonstrated, and they felt the postoperative increase in local heat to be due to loss of sweating and evaporation which normally cools the skin. Postoperative chemical changes in femoral venous blood, noted by McMaster [338] in dogs subjected to unilateral lumbar sympathectomy, were a lower carbon dioxide and a higher oxygen content on the operated side; there were no differences, however, in the lactic acid or sugar content. He concluded, therefore, that the changes in volume of the gases in the blood were not of metabolic origin but due to an improved blood flow. Since the chemical differences disappeared after a few months, McMaster believed that physiologic readjustments must take place, restoring the sympathectomized side to an essentially normal state.

Evidence that the flow of blood is actually and permanently increased by sympathectomy is, however, presented by Herrick, Essex, and Baldes,[339, 340] who noted that the blood flow in the femoral artery of dogs after unilateral lumbar sympathectomy was doubled and remained so for as long as 34 months after operation.

From observations on the healing of experimental fractures in animals subjected to unilateral ganglionectomy, it appeared to McMaster and Roome,[341] Zollinger,[342] and Key and Moore [343] that the operation had but little or no effect in hastening osteo-genesis. Cartilage defects produced in dogs by Key and Moore healed as readily on the unaffected as on the operated side, and these workers concluded that their observations offered no evidence, either for or against the use of sympathectomy for arthritis.

Although sympathectomy produced a "curious relief from pain in many instances" in cases of atrophic arthritis seen by Kinsella,[298] it did not prove sufficiently valuable in his opinion to justify its continued use. One patient, so treated by Johnson, Scupham and Gilbert, was not relieved and the arthritis progressed. A patient of Peet, Kahn and Allen [344] whose pains were relieved only after chordotomy, was unrelieved by previous sympathectomy.

However, " gratifying results " were obtained by one of Kerr's [345] patients with polyarthritis. Spurling and Jelsma [346] reported results in eight cases of chronic arthritis, of 2 to 15 years' duration, in which pain was a dominant symptom. In four cases the lumbar, in one the cervicothoracic, and in three both chains were removed. In seven of the eight cases the patients thought the benefit obtained justified the operation. The results were " highly satisfactory " in cases of periarticular, but with little or no evidence of osseous, injury; results were " reasonably satisfactory " as far as pain relief was concerned in cases of moderate articular involvement and " unsatisfactory " when ankylosis and joint destruction were present. Ten patients were subjected to sympathectomy by Flothow and Swift.[347] Seven of these patients were " distinctly improved," especially as to relief of pain. In three cases no significant result was obtained.

Henderson and Adson [348] have reviewed results of sympathectomy for 41 patients with atrophic arthritis treated by them in collaboration with Rowntree, Hench, and Craig. " Marked improvement " was obtained by 20 of the 41 patients. For this group the average age at onset of the disease was 21 years, and the average duration 58 months. Eleven patients obtained but slight improvement; their average age at the onset of the disease was 29 years and the duration of the disease 76 months. In six cases failure resulted; the average age at onset was 28 years and average duration of symptoms 92 months. In cases of long standing disease and deformity, sympathectomy was of no value. Best results were obtained by young patients whose disease was of relatively short duration. In very carefully selected cases the procedure may give distinct relief.

All workers agree that the suitable case is that of a young patient who has cold, clammy extremities, whose arthritis is only, or chiefly, in the hands or feet, and in whom marked articular change has not yet occurred. While mobility may be increased and swelling reduced, the relief of pain is the chief result. Suitable cases can be accurately selected by noting whether or not temporary relief follows trial injections of acetylcholine hydrobromide (Spurling and Jelsma [346]), novocain, or use of other strong vasodilators (Flothow and Swift [347]).

Histologic studies have been made by Craig and Kernohan [349] of sympathetic ganglions removed from 46 patients who had arthritis. Although changes were seen, they were comparable only to those found in ganglions removed at necropsy from patients unaffected by arthritis or by derangements of the sympathetic nervous system. Nothing was found therein to explain the vasomotor disturbances of arthritic patients. They concluded that the noxious agent causing the disease does not act directly on the sympathetic ganglion removed, but since removal of such ganglions frequently leads to improvement of blood supply to the affected limbs, it would seem that the ganglions act simply as relay stations for impulses from higher centers affected by the disease.

Chordotomy. A man, aged 20 years, who had atrophic arthritis of

three years' duration, suffered severe pain in an arm, shoulder, and in the lower extremities. This pain was not relieved by usual measures or by sympathectomy, but it was almost completely relieved following bilateral cervical chordotomy, by Peet, Kahn, and Allen.[344] Pain was abolished without risk of respiratory paralysis by sectioning the tract at the third cervical segment on one side and approximately the eighth cervical segment on the other. (The patient had no pain when lying in bed, according to a personal communication from Kahn, but had "excruciating pain" on attempted motion of knees. In acute arthritis or acute exacerbations of chronic arthritis there may, for a matter of days or a few weeks, be considerable pain particularly on motion; even so, some relief is practically always afforded, at least temporarily, by the usual measures. When chronic intractable pain occurs in "chronic rheumatism," and when narcotics are required, the admonition of Rynearson and Hench (1931) to "suspect malignancy in 'chronic rheumatism' requiring morphine" is in order. Although chordotomy was well borne and succeeded in its purpose in this case, it would seem to be a very radical procedure, and one that is rarely indicated.—Ed.)

Acupuncture. Analgesia lasting three to four days can be provided in the majority of cases of painful arthritis by acupuncture, an old remedy still favored by Ferreyrolles.[350] Relief is not dependent on anesthesia, as analgesia can be obtained using empty needles.

Splenectomy. Chronic atrophic arthritis is frequently associated with anemia and with adenopathy, less frequently with hepatomegaly and splenomegaly. While the syndrome of chronic arthritis, splenomegaly, and leukopenia may represent either "adult Still's disease" or the coincidental association of arthritis and early Banti's disease, Felty (1924) believed it represented a distinct clinical entity. Hanrahan and Miller[351] performed splenectomy in such a case—the patient being a woman, aged 50 years, who presented an atrophic arthritis of 5 years' duration, an enlarged spleen, palpable liver, anemia (3,450,000 erythrocytes), and a leukopenia (800 cells) with a relative lymphocytosis (86 per cent). Culture of the spleen was negative after 5 days. It weighed 525 gm. (normal, 150 gm.). Hyperplasia of endothelial cells lining dilated sinuses, and increased numbers of plasma cells in the pulp spaces, were seen. A specimen of liver at biopsy revealed fatty changes in the central zone and moderate round cell infiltration along portal vein radicles, limited to the periphery of the lobule. Within three weeks of the operation the patient noted improvement. Four months later, she was still much improved; anemia was not present and the leukocyte count was 10,000 per cubic millimeter.

It is recalled that Chauffard, in 1896, and Herringham, in 1909, called attention to the association of arthritis in adults with splenomegaly and hepatomegaly. Anemia was not emphasized. In 1897, Still noted arthritis in children with anemia, enlarged lymph nodes, and enlarged spleens, but he did not mention hepatomegaly. Others have since reported cases of arthritis associated with various types of reticulo-endothelial response, with

leukopenia or leukocytosis. While it is well to point out such variations, it seems unwarranted to give each combination a new name (Hench [352]). It is not clear whether these reactions represent a complication or a defense mechanism on the part of the reticulo-endothelial system. If the lymph nodes are the first line of defense and the spleen and liver the second defenses, Hench believes one should think twice before advising splenectomy. Only temporary benefit was noted by him in one such case, probably the nonspecific temporary improvement any surgical operation may provide. (For another such case see also Craven, E. B.: Jr. Am. Med. Assoc., March 17, 1934.) The adenopathy and splenomegaly would seem to Hench to support the infectious theory, for such tissue responses whether they are complications or defense reactions, are more suggestive of reaction to infection than to a metabolic or endocrine disturbance. (In connection herewith should be considered two cases of lymphatic leukemia producing symptoms like rheumatic fever; they will be described later.—Ed.)

Periarticular Bone Puncture. An elderly woman, who had long suffered with an atrophic polyarthritis which had been unrelieved by periods of rest, fell and fractured a femur. After the bone healed, Mackenzie (1931) noted that the patient's arthritis was no longer painful. Recalling that in atrophic arthritis pathologic changes are present in bone and bone marrow as well as in articular structures, Mackenzie pondered on the possible benefits of deliberate " experimental bone fracture " or bone punctures. He instituted the procedure in more than 60 cases, with interesting results.[353] An opening is made with a large bit, or a ¾ inch trephine, into (for example) the lower end of the femur and upper end of the tibia Bone marrow flows out like thin oil, due probably to fatty degeneration of marrow. Marked relief of pain, increased joint function, and increased erythrocyte count were noted. In some cases the procedure seemed to be " curative."[353] (Charbonnel, in Bordeaux, has reported similar results in one case, 1933.)

Reconstructive Surgery. In most patients chronic arthritis sooner or later reaches the stage of quiescence. A fortunate number will have little or no deformities, or deformities of but little significance. Some may have one or two joints seriously deformed; others are grievously deformed and appear " hopelessly crippled." At the hands of the skilled orthopedist much can be done to restore hope, motion to the joints, and a means of livelihood. What can be done and the optimal time for doing it are matters of great importance to the physician in attendance. The indications for any methods of orthopedic reconstruction of such joints are again set forth by Wilson and Osgood,[354] and by Stump.[355, 356] Reconstructive surgery should not be undertaken until the joints have been free from active disease for at least six months. It is at times difficult to determine whether activity has ceased. The presence or absence of pain is not an absolute guide (Wilson and Osgood). Even after the active disease has ceased a patient may complain of pain, due not to inflammation but to stretching of adhesions, or of a

fibrosed capsule, or to strain on an injured joint. The problem of correction is a difficult one for the patient who may have to endure long hospitalization and multiple operations, but treatment is amply remunerative.

Remissions; Usual and Unusual. The course of atrophic arthritis is characterized by exacerbations and remissions. The more common causes of exacerbations are overactivity, weather changes, the menses, and intercurrent infections such as colds and influenza. "Natural remissions" follow rest and the onset of warm or stable weather. The latter months of pregnancy may be accompanied by a marked recession of arthritic activity.

Remissions, unfortunately too often temporary, are induced by many types of treatment as these pages indicate, but the true value of any treatment must take into account natural remissions. Typhoid vaccine may produce a remission, sometimes short lived, sometimes prolonged. Wilberforce [357] noted a case, of a woman of 57 years with advanced painful deformities, in which a striking remission set in during an attack of typhoid fever and lasted more than a year. Many have noted remission induced by relatively unrelated surgical procedures (Kinsella [298]).

A "new cause" of remissions has been reported by Hench [358] who made observations over a period of four years on the effect of intercurrent jaundice on the rheumatism (arthritis, fibrositis, sciatica) of 16 patients. In some cases the jaundice had been induced by cinchophen, in others however, it was unrelated to drugs. Coincident generally with the onset of jaundice, 14 of the 16 patients obtained partial, or more usually, complete relief of pain for variable periods of several weeks to many months, and in some cases even years. In several cases marked, even complete, reduction of swelling was noted. To this observer the therapeutic implications seem obvious; it would be gratifying if one were able to repeat nature's miracle, to provide at will a similar beneficence by the use of some nontoxic accompaniment of jaundice effective in available concentration. (These observations have been confirmed by Sidel and Abrams, New Eng. Jr. Med., 1934, ccx, 181–182.—Ed.)

Prognosis and Results of Treatment. Many patients, indeed many physicians, have the impression that "nothing can be done for atrophic arthritis." This pessimistic point of view is wholly unjustified, as statistics show. The foregoing pages indicate that success rarely follows the institution of one simple form of treatment. The disease does not rapidly fade as the result of one therapeutic tour de force. The patient must be taught the importance of the multiple aspects of his disease and its treatment. He must appreciate that a long period of training is necessary. But he can generally be assured that wisely conducted treatment, based on a composite program comprehensively applied, leads to success (Minot [268]).

Beneficial results follow the isolated use of many of the approved methods of treatment in from 50 to 70 per cent of the cases. When a number of measures are instituted, notable improvement and reasonably early cessation of the disease occur in 70 to 80 per cent of cases. In Lipkin's [206]

series of 200 patients with chronic arthritis, 21 per cent had "recovered," 32 per cent had marked and 20 per cent moderate improvement. In Matz'[192] series, 76 per cent were "improved." Minot cites figures from Sweden and from London to the effect that within three years 60 per cent or more of all patients were working comfortably at their old jobs. Of 50 patients (half with atrophic and half with hypertrophic arthritis) who followed Minot's[286] instructions faithfully for four years, 85 per cent were definitely better and in 60 per cent the disease had apparently been arrested for two years or more. This was in contrast to results for those who did not follow treatment faithfully, of whom only 35 per cent seemed to be definitely better.[286] Osgood[187] believes that chronic arthritis is a controllable disease, and that there are few chronic diseases for which more can be done. Such high percentages of recovery or arrest can "certainly not be attained with cancer, almost certainly not with chronic heart disease, and probably not with chronic tuberculosis," the three most common chronic diseases in his state.

Hypertrophic Arthritis

It has been explained that the term "hypertrophic arthritis" as used herein refers to the clinical syndrome sometimes designated senescent arthritis, degenerative arthritis, or osteo-arthritis. It signifies a disease entity and not a roentgenographic pattern also seen in certain stages of traumatic, gouty, hemophilic, gonorrheal, or other types of arthritis, including even the late stages of atrophic arthritis, especially in weight-bearing joints. It has been stated that although some (Willcox,[198] Knaggs,[197], Clawson and Wetherby,[210, 211] Smith[276]) believe it is but a variation of the disease which in younger or less robust individuals is manifest as atrophic arthritis, the majority insist that it is a separate entity, differing in cause, in clinical, immunologic, pathologic, and roentgenographic features, in treatment and response thereto, and above all in prognosis. Unlike a squeaky wheel, the creaky joints of hypertrophic arthritis do not get as much attention as the generally less noisy but more painfully diseased joints of atrophic arthritis. Few articles concern hypertrophic arthritis alone; we learn of it as its contrasting relationships to its more potent cousin are mentioned, or when it is used in series as a control for atrophic arthritis.

Symptoms and Course. Its clinical, pathologic, immunologic, and roentgenographic characteristics have thus already been briefly touched on. For a fuller summary reference can be made to the Primer.[188] In hypertrophic arthritis, prodromes are not so common or striking, for here we are not dealing with a toxemia with its widespread manifestations, or at least if a toxemia is involved it is much less formidable and the disease's manifestations tend to be peculiarly localized. Such premonitions as there may be, Painter[267] feels, include the following: lassitude, headache, sluggishness of intestinal activity, and frequency of micturition, suggesting an impaired digestion and a disturbance of metabolism. Many of the women in Lipkin's

series noted nervousness, dizziness, tingling of fingers, hot flashes, and other "menopausal symptoms." Thirteen women exhibited Heberden's nodes, the earliest at 36 years of age. Only one man had such nodes. The lumbar spinal column and knees were involved next in frequency, and the cervical spine, shoulders, and hips were less frequently attacked. Only half as many (53) patients with hypertrophic arthritis consulted Lipkin as those with atrophic arthritis (113 patients).

In Matz' series there were more cases (213) of hypertrophic than of atrophic (172) arthritis. Each of the patients in the former had an average of 2.8 involved joints as compared to 3.7 joints in the atrophic group. Only 15.5 per cent of those with hypertrophic arthritis gave a hereditary or familial history of joint disease. The disease may manifest itself much earlier than is generally supposed, according to Matz, in whose series the average age of onset in 213 cases was 31 years. Forty-five per cent were above, 23 per cent below standard weight. Constipation was generally absent. Fifty-three per cent gave a history of focal infection (as compared to 83 per cent in the atrophic cases). In 26 per cent of cases the onset of symptoms was acute. The average number of attacks was 2.7 per patient, although half of them had only one attack. The average duration of the disease was 132 months. (From some of these statements it seems likely that at least some of the cases included were roentgenographically but not clinically of the hypertrophic type.—Ed.)

In Eaton's series more women (76) than men (47) were painfully affected. Although about 23 of 123 patients noted pain between the ages of 20 and 40, the majority were attacked between the ages of 40 and 60. Many patients with Heberden's nodes remarked on a familial tendency thereto. Only about 14 per cent were underweight, 50 per cent overweight. Quite a number lost weight during their illness. Vasomotor phenomena, such as "dead fingers," patchy erythemas, urticarial wheals, and the symptoms of nervousness, restlessness, excitability, loss of mental vigor, and exaggeration of tendon reflexes, were noted and were more frequent among women than men affected with hypertrophic arthritis; they were not present, however, as often as in cases of atrophic arthritis. Sweaty skin was seen more often among men, but less frequently in both sexes than in cases of atrophic arthritis. The disease involves wrists, elbows, and ankles much less frequently than does atrophic arthritis. Eaton [209] and Ray [359] have reviewed its characteristics at its favorite sites of predilection. A painful great toe, with hypertrophic changes, may be the analogue of a Heberden's node (Ray).

The hip is fortunately not involved as often as fingers, knees, and spine, but when attacked it is likely to cause more disability. Of 302 hip joints of persons more than 20 years of age who were studied roentgenographically for various diseases by Brailsford,[360] 203 showed arthritis: "osteoarthritis" in 130 cases, "chronic arthritis" (atrophic?) in 73.

Roentgenographic Picture. The studies of Scott [201] and Rigler and Wetherby [202] have been commented on (p. 1498).

Pathologic Changes; Joints. The characteristic pathologic changes—cartilage fibrillation and degeneration, osteophyte production and destruction, and eburnation of subchondral bone—have been reviewed by Eaton. Knaggs' [197] opinion regarding the pathologic discreteness of the disease has also received comment (p. 1501).

Pathologic Changes; Nodes. It has been noted that subcutaneous fibrous nodes are not to be expected in hypertrophic arthritis (p.).

Laboratory Data; Blood Counts, Blood Volume, and Blood Chemistry. In his studies on blood in arthritis Eaton included both atrophic and hypertrophic types without distinction. Since abnormal counts were found in all but three of 250 cases, we are left to assume that changes in cells in hypertrophic arthritis are consistently present and similar to those in atrophic arthritis. (This is not the usual belief and it is unfortunate that the types were not studied separately.—Ed.) The filament-nonfilament count may be altered in hypertrophic, as well as in atrophic, arthritis, but it is much more likely to be normal in the former and rarely if ever normal in the latter (Steinbrocker and Hartung [214]). The blood volume (generally above normal in atrophic arthritis) was found by Sparks and Haden [218] to be 6.7 per cent below the average normal in 15 cases of hypertrophic arthritis, probably because of associated obesity. As we have noted, the phosphatase test is apparently normal (Race [221]), and the sedimentation rate is either normal or but slightly elevated, 20 to 30 mm. in one hour (Dawson and Boots [213]). In certain cases it may approach values more frequently seen in cases of atrophic arthritis (Oppel, Myers and Keefer [62]).

Routine studies of blood chemistry in cases of hypertrophic arthritis show no significant changes in serum calcium or phosphorus, in calcium and phosphorus metabolism (Bauer, Bennett and Short [220]), or in blood sugar, urea, or creatinin. Some (Eaton [219]) report a tendency to high normal or slightly elevated values for blood uric acid.

Etiology and Pathogenesis. Opinions on the cause of hypertrophic arthritis are that it is due to: (1) infection, (2) degenerative process of age, (3) trauma, (4) a metabolic disturbance, (5) an endocrine disturbance, and (6) circulatory disturbances associated with arteriosclerosis or other causes. Age and trauma are the factors most often incriminated, and those who believe it is an infectious disease are in the minority. Indeed, positive findings in the voluminous studies used to support the infectious theory of atrophic arthritis gain their chief distinction in that similar studies in hypertrophic arthritis are generally negative. Thus, blood or joint cultures in hypertrophic arthritis were found to be negative in 27 cases by Gray, Fendrick, and Gowen,[107, 108] as they have been in general by others. There was practically no agglutination of streptococci in these cases, nor in about 60 cases seen by Dawson, Olmstead, and Boots,[229] nor in 44 cases studied by Nicholls and Stainsby.[231a] Only 15 per cent of 28 cases seen by Keefer, Myers, and Oppel [140] exhibited streptococcal agglutinins. In 23 cases tested

by the latter with streptococcal nucleoproteins, skin reactions were negative in 63 per cent; slightly positive in 37 per cent.

In spite of these findings, several workers favor the infectious theory. Thus Crowe [361, 362] feels that trauma and deformity are not very important predisposing factors, and Ray [352] believes that while age and trauma play some part, hypertrophic arthritis is "undoubtedly associated with the absorption of toxins from a sluggishly acting bowel." Streptococci are blamed by some (Burbank, Crowe, Clawson, Wetherby, Ryerson, Willcox) on the basis of skin tests, complement fixation tests and occasionally positive blood cultures. Others (Elmslie,[363] Smith [276]) are less specific and state the belief that it is due to bacterial or food toxins of intestinal or other origin. Thus, while admitting that there is little or no proof that bacterial infections can cause osteo-arthritis, Elmslie feels that they can initiate changes which, altered by other factors, eventually simulate osteo-arthritis. Ryerson believes infected teeth are the chief focus in cases of hypertrophic arthritis.

As causative factors, age and trauma are generally considered coöperative and not regarded separately. Thus, Miller [133] and others consider "age" merely the opportunity for mild, long-continued trauma of posture, occupation, and recreation. The radiologic and symptomatic manifestations of hypertrophic arthritis have long been correlated with the decades between 40 and 70, roentgenologic changes being noted rarely before 40, generally between 45 and 50, universally after 60, with symptoms often remaining absent or not appearing until some months or longer after radiologic alterations. Just as symptoms may lag behind roentgenologic changes, so the latter lag behind earlier but unmistakable pathologic changes, as shown by Keefer [364] who studied 100 consecutive knee joints of 67 men and 33 women at necropsy. Gross changes identical with those of hypertrophic arthritis were not seen in any of six cases in which patients had been between the ages of 1 and 29, but were seen in 66 per cent of six cases between 30 and 39 years, in 100 per cent of nine cases between 40 and 49 years, in 95 per cent of 20 cases between 50 and 59 years, in 100 per cent of 28 cases between 60 and 69 years, in 94 per cent of 19 cases between 70 and 79 years, and in 91 per cent of 12 cases in which patients had been more than 80 years old. The most frequently involved surfaces of the joint were those of contact. Thus the sites of change were as follows: patella in 81 cases, interpatellar groove in 65, lateral tibial condyle in 64, medial tibial condyle in 55, medial condyle of the femur in 50, and lateral condyle of the femur in 41. Keefer concluded that hypertrophic arthritis is due to aging of joint tissues, but that the lesions produced thereby may be exaggerated by trauma, hemorrhage, infection or urate deposits. (It is unfortunate that these interesting studies were not correlated with clinical data on presence or absence of joint pain.—Ed.)

The trauma which produces hypertrophic arthritis may be of the mild, long-continued variety from strains, or minor injuries, from mechanical or anatomic derangements, for example, in the hip (Elmslie); or it may be of

the more acute type. Young Olympic athletes frequently exhibit osteophytes in the joints most used (Miller [133]).

Pemberton believes that hypertrophic arthritis, just as atrophic arthritis, may be due to defects in peripheral circulation and derangements of metabolism. Alterations in peripheral blood flow and in configuration of the colon are noted by him in both types, and while the two should be separated in consideration of symptomatology, pathology, and prognosis, they may be somewhat closely related etiologically and therapeutically. Goldhaft and Pemberton (1930) previously produced pathologic changes, chiefly of hypertrophic but also of an atrophic type, in the patellas of dogs subjected to ligation of the patellar arteries. To them it is difficult to see why, in man, atrophic arthritis should largely appear in middle life and hypertrophic arthritis later unless these diseases represent different age responses to perhaps identical exciting factors. The ligation experiments were repeated [365] on dogs of various ages, to note the influence of age in modifying response to a single insult. Hypertrophic arthritis was produced slightly or not at all in young dogs, but was produced in mature dogs. Thus age seems to govern response to the more direct agent, the vascular insult.

In view of these experiments in which hypertrophic changes are subsequent to diminution of arterial blood supply, those of Bernstein [366] are of interest. Venous congestion of the lumbar spine was produced in five dogs by ligating the lumbar veins. After two years, new bone formation on the vertebral bodies, but not on the margins, and cartilage proliferation were noted. In one dog passive congestion of the knee joint was produced by ligating branches of the femoral vein. Nine months later the synovial membrane showed granulation tissue and pannus formation over articular cartilage, with necrotic areas in the cartilage.

Heberden's nodes develop, according to Elliot,[367] from the predisposing factors of disturbed circulation and disturbed calcium metabolism, with trauma acting as an aggravating factor. (While predisposing and aggravating factors are noted, the inciting factor is not noted.) As stated previously (p. 1515), the skin temperature is reported as sometimes being lowered and the capillary blood flow slowed in cases of hypertrophic as well as of atrophic arthritis. Constriction, tortuosity, and a diminished number of capillaries are seen less frequently in cases of hypertrophic arthritis (Kovacs, Wright and Duryee [263]).

Elliot believes that exacerbations of pain and tenderness in Heberden's nodes are related to intestinal irregularity, and that absorption of bacteria or their products is favored by elongated atonic colons. We have noted Eaton's observation that no differences could be noted in the eating habits of patients with hypertrophic or atrophic arthritis or of nonarthritic persons.

Because hypertrophic arthritis so frequently appears in women about the time of the menopause, it has been called menopausal or climacteric arthritis, the inference being that it is of endocrine origin. With others, Miller [133] believes that the menopause is not the chief factor but that obesity which may

go with it is, and that "menopausal arthritis" is in reality hypertrophic arthritis from the trauma of obesity. Ellman [291] approves the endocrine hypothesis. According to Duncan,[368] hyothyroidism may be associated with and aggravate hypertrophic arthritis. Stigmas of hypothyroidism were seen by Hall and Munroe [254] more often in hypertrophic than in atrophic arthritis. In 108 cases of the former, metabolic rates were below — 10 in 50 per cent, below — 15 in 34 per cent.

Experimental hypertrophic arthritis can be produced, as shown by Key,[36, 369] by a wide variety of methods in which articular cartilage is injured, primarily by mechanical, chemical, or thermal agents or secondarily by functional trauma in a disorganized joint in continued use. The pure functional and senile theories are inadequate, however, as clinical data show, and no one has found the cause of the primary injury to articular cartilage that initiates hypertrophic arthritis in man.

Conclusions on Etiology. From the radiologic standpoint there are several kinds of hypertrophic arthritis: that associated with Charcot's disease, hemophilia, gout, Paget's or Perthe's disease, acute or chronic trauma, or with infections. Excluding these factors, there remains the group under discussion, the clinical syndrome of "hypertrophic arthritis." The exact cause of this hypertrophic arthritis is obviously not known, but it is predicated largely on age, incited or aggravated by a variety of traumas, and perhaps is secondarily influenced by infection.

Treatment of Hypertrophic Arthritis. Many believe, as does J. L. Miller, that the most important part of treatment is to explain to the patient the difference in the prognosis of the disease he actually has from that he thinks he has, and that hypertrophic arthritis (unlike atrophic arthritis which the patient fears) is essentially not an ankylosing, severely crippling, progressive disease. This done, many patients will ask for no other treatment but will bear their difficulties philosophically.

Removal of foci is believed by most to be of no real value in altering the course of the disease (Allan,[370] Miller [133]). Sinus infections, however, were treated by Hurd [272, 273] with reported benefit to joints in this type of arthritis also. Miltner and Kulowski [283] found infected foci in 95 of 100 cases, especially infected teeth, but removal of foci resulted in no improvement in 91 cases, some improvement in nine, and a "cure" in none. Haden [228] concedes that infected foci should be removed as a matter of general principle without expecting specific results.

When obesity is present, a weight-reduction diet is generally advocated to reduce trauma therefrom (Miller [133]). Ray agrees with Pemberton on the value of avoiding unnecessary metabolic burdens and favors a diet low in calories even in the absence of obesity. On the grounds that the blood uric acid is likely to be high (a disputed point), he urges restriction of purine and the use of supposed intestinal antiseptics (guiacum and sulphur: Bulgarian soured milk). Colonic irrigations are used by Smith.[276] A diet high in vitamin B, low in carbohydrates, but adequate in protein is favored

by Elliot.[367] Most workers consider diet of minor importance in this type of arthritis unless obesity is present.

Vaccines are used by several (Burbank,[224] Crowe,[361] Thomson,[293] and Ryerson [269]). Of 245 patients treated by Crowe and Young [294] with vaccines and by removal of foci, 7 per cent became symptom free, 33 per cent were "much improved," 46 per cent "improved," and 14 per cent were unrelieved. In a later report of 125 patients with osteo-arthritis of the hip, Crowe reported 56 per cent were benefited by such treatment. Progressive changes were presumably halted and pains relieved. Thomson also used Crowe's vaccine with benefit. Clawson and Wetherby used their vaccine for both types of arthritis, indiscriminately. Dawson and Boots, and Holbrook and others see no excuse for vaccine therapy in hypertrophic arthritis.

Endocrine Therapy. Thyroid therapy by Hall and Munroe [254] seemed to assist other measures in bringing relief to 49 per cent of 116 patients. Possible stimulation of pelvic organs may in part be responsible for the relief obtained by Robinson's [279] patients with degenerative arthritis and endocervicitis who were treated by pelvic diathermy and ionization.

Physical Therapy. The usual methods of heat, massage, and mild exercises are approved. A judicious ratio between rest and moderate activity is generally advised, with a little more emphasis on rest and the use of crutches, canes, or caliper splints as necessary to reduce trauma to involved hips or knees (Ray,[359] Miller [133]). Manipulation is favored by Douthwaite [326] for certain affected hips, but it is decried by Crowe who also does not favor massage or calipers. For stimulating circulation in Heberden's nodes Elliot [367] advises violin playing or similar use of the hands, and he reports the reduction of nodes by the pressure of adhesive or other plaster, bandages, or metallic bands intermittently applied.

Roentgenotherapy. Radiologic treatment for hypertrophic arthritis in various joints, especially the spine and hips, is favored by several (Kahlmeter [22]). Langer [323] treated 138 such patients, with reported benefits. Scott [201] believes that poor results have been due to improper dosage. Treatments by roentgen rays are the method of choice of Watt,[371] Hernaman-Johnson,[325] Kempster,[372] and Batten.[373] Forty per cent of 194 patients were symptomatically cured or "markedly relieved"; 23 per cent were "improved," 37 per cent were not (Watt, see Scott [324]).

However, in some cases improvement is not lasting (Douthwaite.[326]). Ten of 24 patients with hip disease got considerable relief of pain for six months, but then suffered a relapse. Five, however, were remarkably relieved from one and a half to two years. Hips seem to respond better than other joints: of 10 patients whose fingers were treated by Douthwaite, none were relieved. Of 10 with painful knees, three were relieved. While some believe roentgenograms show improvement (Hernaman-Johnson [325]), others see no change (Woods,[374] Douthwaite).

Surgical procedures are rarely indicated; when necessary, they may give

relief. Groves,[375] has outlined the indications for cheilotomy (removal of osteophytes), arthroplasty, arthrodesis, excision, or osteotomy. Cases of monarticular hypertrophic arthritis in which Bernstein [336] performed synovectomy were among those in which "best results" were obtained.

Spondylitis

Backache and Spondylitis. Backache, particularly low back pain, may arise from a number of causes of which arthritis is the most common. Atrophic or hypertrophic arthritis of the spine was the cause of "backache" in 46 per cent of 500 cases seen by Duncan [368] and of 36 per cent of 668 cases seen by Shands and Oates.[376] The differentiation of the types and causes of backache, with details of the examinations necessary, have been considered by several (Bankhart,[377] Ely,[248] Durham,[378] Brailsford,[360] Wheeler,[379] Moore and Kyle,[380] Holbrook, Jepson,[381] Nicola [382]). Conditions from which arthritis must be distinguished as the cause of backache are: "sacro-iliac strain or displacement," lumbosacral strain, acute and chronic lumbar strain, "neurotic spine," the "constitutional or structurally weak back," "kissing spinous processes," true lumbago, Pott's disease, fractures, spondylolisthesis, congenital anomalies, cord tumors, and malignancy. It is beyond the scope of this review to discuss such differentiation. Next to arthritis in frequency, painful backs are due to the constitutionally weak or mechanically defective back as found in the woman who, for years, feels comfortable in bed but develops a progressive backache during the day, continues to show no roentgenographic alterations, but is found to have weak back muscles that favor a constant posture of chronic spinal hyperextension. Thirty-four per cent of Duncan's 500 patients suffered therefrom. (Many would argue that postural joint strain is a much commoner cause of backache than arthritis and that postural back strain precedes localized traumatic arthritis in the lower spine in a high percentage of cases.—Ed.)

According to Bankhart, patients who suffer with long continued backache almost invariably develop a "neurotic spine," a neurosis superimposed on genuine organic or structural disability. It may vary in degree from a more or less diffuse hyperesthesia to a profound neurasthenia. Its characteristic features are superficial and variable tenderness in contrast to the constant and definitely localized pain of the associated organic condition.

Several have reiterated the well-known fact that while a roentgenogram is absolutely essential, it does not always reveal the cause of back pain. The majority of such sufferers have real trouble, and are not malingerers, but their trouble may not cast a roentgenographic shadow. Roentgenograms of painful backs must be subject to most careful interpretation, as much lipping may be present without symptoms, and vice versa. Even when alterations are noted in the roentgenogram they may not be the cause of the backache.

Types of Spondylitis. The present tendency is to place several described varieties, excluding special forms (tuberculous, typhoid, and so forth)

under two headings: atrophic spondylitis and hypertrophic spondylitis. Atrophic spondylitis is synonymous with the British Committee's [383] term, spondylitis ankylopoietica, and probably includes the forms called "spondylose rhizomelique," "Marie-Strümpell type," spondylitis ossificans ligamentosa (Knaggs [197]), and "infectious spondylitis." It probably compares with atrophic arthritis in other joints. It is characterized by osteoporosis of vertebrae, often early osteoporosis and destruction of sacro-iliac segments, secondary ossification of ligaments, and ankylosis producing the "bamboo-spine." Early roentgenograms may show little or nothing but atrophy of bone. Later, density of affected facet areas and sharply defined shadows along the course of ligamenta flava may be seen. Still later, small osteophytes and bony ankylosis occur. Those who wish to distinguish the variety in which the anterior common and other ligaments are early and strikingly ossified, separate it from the general head of atrophic spondylitis.

Hypertrophic spondylitis (senescent spondylitis, spondylitis osteoarthritica, von Bechterew type, degenerative arthritis of the spine) is comparable to hypertrophic arthritis elsewhere and is characterized by early, and sometimes gross, lipping of vertebrae with formation of exostoses from vertebral bodies and processes. Knaggs has separated a type or subtype as spondylitis muscularis, which is characterized by kyphosis, immobility, weak muscle tone, not much pain or tenderness, and atrophy of intervertebral disks with eventual lipping and spurring of vertebral margins.

Of the 243 cases of spondylitis studied by Shands and Oates,[376] 32 per cent were of the atrophic type. Of these 78 cases, in 12 there were clinical signs and symptoms but negative roentgenologic findings, in 50 atrophy of bone and blurring or haziness about facets and intervertebral disks, and in 16 ligamentous calcification (Marie-Strümpell type). Sixty-seven per cent were of the hypertrophic type, one being of the von Bechterew variety and the rest of the "true type." Of the total group 58 per cent of the patients were men, 42 per cent women. Of the patients with atrophic arthritis, 56 per cent were women, and of those with hypertrophic arthritis 41 per cent were women. The earliest lesions are in the lower portion of the spine, thus the average age of patients with sacro-iliac and lumbosacral involvement at the onset of the condition was 33 years, for those with thoracic and lumbar involvement 42 years, and for those with cervical involvement 46 years. Trauma seemed to be a factor (40 per cent) when the lower regions were involved, but was less so (22 to 24 per cent) for the two higher regions; rarely was it a factor in cases of the Marie-Strümpell type. Pain projection was much more common among patients with cervical (64 per cent) and sacro-iliac (65 per cent) involvement than for those with thoracic involvement (20 per cent), and it occurred in 43 to 48 per cent of cases in which the lumbar or lumbosacral regions were attacked. When the cervical area was involved, marked symptoms were often present without signs. The reverse applied when the lower regions were affected.

Three types of spondylitis are recognized in the study of Holbrook,

Stecher, and Hayden [384]: "primary spondylitis," types A (without ankylosis) and B (with ankylosis), and hypertrophic spondylitis, included with other varieties of generalized hypertrophic arthritis. Type B is considered as identical with Knaggs' spondylitis ligamentosa ossificans. They looked on type A as an unrecognized syndrome, characterized by its appearance in young men, and progressing from an insidious onset to a poker spine, with negative roentgenograms of the spine but with destruction of cartilage and fusion at the sacro-iliac joints. (In many cases of atrophic spondylitis, roentgenographic alterations, aside from or including bone atrophy, may be long delayed. Is not this "new syndrome" but a recognized variant of atrophic arthritis?—Ed.)

Of 386 patients with atrophic and hypertrophic arthritis, 60 were found by Bisgard [385] to have hypertrophic arthritis of the cervical spine, with localization of the lipping to the fifth, sixth, and seventh cervical vertebrae in most cases. Thirty-one had occipital or suboccipital headaches, at times, which were made worse by damp, cold weather. Thirty-eight had pain, tenderness, or stiffness in the neck or a sense of fatigue in the neck and shoulders. Eight had neuralgic pains ("neuritis") in shoulders or arms, but radiation was generally not segmental. Sensory disturbances (tingling, burning, or numbness of arms) were present in nine cases (in only two of which was the distribution along nerve roots or trunk); only four patients had motor disturbances (muscle weakness). Atrophy of muscle in arms, or at thenar and hypothenar areas, was occasionally seen. One patient had associated hiccups. Many patients with extensive cervical arthritis, however, are free of symptoms.

A particularly resistant and progressively painful spondylitis must always be suspected of being the result of vertebral malignancy. A man fell and a "backache" developed which persisted for 18 years. He then experienced severe and constant low back pain which was unrelieved by the usual treatments and required morphine. An adenocarcinoma was found by Mason-Hohl.[386]

Etiology. The same theories apply here as to arthritis elsewhere, with recognition of the fact that trauma plays a particularly active part in any arthritis of the spine. Ely [248] insists that hypertrophic spondylitis is due to "some living organism not bacterial, which usually gains access to the body through the open bone at the roots of dead teeth." Its later habitat is probably the intestines. He conceives the primary pathologic change to be an aseptic necrosis in bone marrow near joints, and that the ensuing arthritis is essentially traumatic. Diverticulitis may be a common cause of spondylitis, according to Brailsford [360] who cited statistics of others as follows: of 100 patients with diverticulosis, 72 had spondylitis; of 100 patients who did not have diverticulosis but who were of the same average age (58 years) only 20 had spondylitis.

Treatment. The treatment in general is the same as that described for atrophic or hypertrophic arthritis, with braces and corsets as necessary.

For painful cervical arthritis Bisgard favors immobilization in a Thomas collar for several weeks with daily traction, and also roentgenotherapy. Rest is not advised by Pockley [387] in cases of "kinked back" or in cases of acute or chronic lumbago. Rapid and complete relief can be obtained in two days in acute cases if the patient has the fortitude to perform repeatedly the movements that cause most pain. The movement most usually effective is that of repeated dorsiflexion, extension of the back as far as possible. In chronic lumbago such treatment is equally good, but it takes a "few days longer."

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EDITORIALS

THE SESSION IN PHILADELPHIA

THE Nineteenth Annual Clinical Session of the American College of Physicians in Philadelphia will long be recalled in the history of the College not only as having set a new mark in the number of those attending the meeting but also as one of the most interesting of our Annual Sessions in the quality of the program offered.

The field of internal medicine is a broad one, but it was fully covered by the Clinic Sessions in the famous medical institutions of this great city and by the carefully chosen papers of the General Sessions. The only difficulty encountered by the visitor lay in making a choice among such a wealth of possibilities, and the only regret was that so many interesting features had to go unvisited for lack of time. There was indeed a question as to whether the feast offered was not too large and varied for even the robust appetite of the College and whether some of the choicest offerings did not go relatively untasted, to the natural dissatisfaction of the chefs. If it were so, it was all a part of that gift for endless hospitality which seems characteristic of our Philadelphia colleagues. To all who gave so freely of their talent and of their time for our instruction and our entertainment, the College owes a debt of gratitude.

To those who were unable to attend, the ANNALS OF INTERNAL MEDICINE will bring during the coming months the chief papers read at the meeting. In our pages these contributions take their permanent place in the medical literature. The Annals can do no more to aid the absentees in retrieving the lost opportunity; but it may and does counsel them to consider the extent of their loss and so lay early plans to attend the Twentieth Annual Clinical Session in Detroit.

THE CERTIFICATION OF SPECIALISTS IN ITS RELATION TO POSTGRADUATE EDUCATION

THE field of prophesy, as all physicians well know, is full of pitfalls, but one cannot contemplate the steady progress of a great movement in our profession without being led to speculate as to its effects upon existing medical customs and institutions. The trend toward certification of all specialists by examining boards under the aegis of the American Medical Association is steadily growing stronger as it gains the adhesion of more and more of the profession. It may well stimulate thought as to its necessary repercussions upon our present medical environment.

In a study of the graduates of the leading medical schools in the United States, Weiskotten found that after a six-year period, from 1920 to 1926,

35 per cent of the total graduates of these schools were partially or completely restricting their practice to a specialty. Perhaps with the increasing crowding in the field of specialism these figures are no longer strictly applicable as indicating the plans of our more recent graduates. Nevertheless it may be assumed that they still roughly indicate the size of the task which is involved in providing really adequate training in the special fields for those who will desire to enter them.

It does of course seem certain that a first effect of elevating the standard of training for specialism will be to decrease the number of those entering upon such training. Such an effect, with an eventual diminution in the number of specialists, may be a gain or a loss. It will be a gain if those who are deterred from specializing are only those who grow faint-hearted at the prospect of further years of serious study, of long hours in the free clinics and on the wards, of tests to be met on the way and of a final examination to be passed. It will be a loss if too many able men are forced to abandon their ambition to specialize only because they lack the money to finance themselves through an expensive postgraduate course. It does not seem unsound to predict that the ultimate true success of the movement for certifying specialists is dependent upon the development of a plan for satisfactory postgraduate education at low cost. In our present system, men of ability who also have sufficient means may obtain satisfactory and systematic postgraduate training either in this country or abroad. A small number of picked men may, through long term residencies and fellowships, obtain valuable but often incomplete training in a specialty in our hospitals and schools. Too many young physicians today, however, are driven to accept as adequate training a year of special internship, a brief period of unsupervised work in the special department of a dispensary, or even a few months in a special course in some graduate school.

It is this last and largest group for which better provision must be made. It seems apparent, since for the most part they must earn a living during the period of training, that they will have to engage in general practice during these years, and that therefore their postgraduate education will have to be confined to a limited period of each day. Moreover, since they cannot pay for this education in money, they will have to find it where the return they can make in professional services will take the place of money.

Those large general dispensary clinics which reorganize themselves so as to provide systematic postgraduate instruction to these young physicians in return for their services will not lack for willing workers, while those which continue to offer nothing more than crowded hours of routine unsupervised work will dwindle away. Funds must be found, it is true, to provide for better equipment, more technical help, and perhaps for some paid instructors in such reorganized clinics. The difficulties in the way are real enough, and not all institutions will be able to solve them. It is not our purpose to propose solutions, but only to indulge in prophecy. Our predictions are

summed up in the statement that there will soon be a rapidly growing demand for adequate postgraduate education acceptable to the various examining boards for the specialties; and that those institutions which reorganize their out-patient clinics to serve as postgraduate schools will be strengthened as a result of this movement, while those who fail to make this adjustment will fall to a lower level.

REVIEWS

(1) *Clio Medica. Japanese Medicine.* By Y. FUJIKAWA, M.D. Translated from the German by John Ruhräh, M.D., with a chapter on the Recent History of Medicine in Japan by Kageyas W. Amano, M.D., DS.C. (Med.) With 8 illustrations. 114 pages. Paul B. Hoeber, Inc., New York. 1934.

(2) *Clio Medica. French Medicine.* By M. LAIGNEL-LAVASTINE and M. RAYMOND MOLINERY. Translated by E. B. Krumbhaar, M.D. With 14 illustrations. 187 pages. Paul B. Hoeber, Inc., New York. 1934.

This valuable series of primers on the History of Medicine is on its way to become a "collection"—something like the Loeb Edition of the Classics—something that every physician will want always on his shelves and occasionally in his pocket. Ten or twelve of these small attractive volumes have already been published. We have had Egypt and Assyria, Canadian Medicine, Medicine in the British Isles, Italian Medicine, Medicine among the American Indians, with other single volumes on the History of Anatomy, Physiology, Internal Medicine and Nutrition. Now we have Japanese and French Medicine. Many other volumes are in preparation.

The late Dr. John Ruhräh has translated from the German the short history of Japanese Medicine by Dr. Y. Fujikawa, that was prepared by the Japanese Government for the International Exposition of Hygiene at Dresden in 1911. Dr. Amano has brought this history up-to-date. Anything that Dr. Ruhräh did was well done and this translation of his is clear and concise. The various chapters deal with the periods in medical history that coincide with the main divisions of the history of Japan itself. The Mythical Period ends with about 97 B. C.—the "old time of the Gods" when "without question the Japanese were on the peninsula of Corea" (p. 13), for it was from Corea that the physician Oyu-Ryoda in 552 came to Japan and brought Corean medicine with him. The Nara Period—those of us who have been in Japan will never forget Nara—was a brief one, only some thirty years. Buddhism had been brought to Japan by the Imperial Court and the Buddhist priests occupied much the same place in medicine as did the Christian monks of the Middle Ages. They even established a charity hospital. The Heian Period boasts of the oldest existing medical book of Japan. It is a compendium of extracts from the Chinese Classics, to which the writer adds observations of his own (p. 11). It reminds one of similar works in the Byzantine period of Greek Medicine—Oribasius or Paul of Aegina. To anyone who loves Japan, this little History of Medicine is full of names that are fragrant with memories of Japanese beauty. The Kamakura Period, with its revival of Buddhism and the development of Japanese national feeling, brings the reader to the feet of the great silent image of Buddha among the Kamakuran trees. The long Yedo Period, not ending until 1867, takes one to Nikko and the Tokugawa Shoguns—to the great temples with their torji and the long avenues of tall, ancient trees. Here, in the eighteenth century, come Japan's first contacts with the Dutch and other Europeans, and the introduction of European medicine. In the recent years of Japan's medical history, there are famous names known to all of us: Dr. Kiyoshi Shiga, who discovered the bacillus of dysentery, Hata, who was associated with Ehrlich and many others.

The book contains a very useful chronological table and a good index of subject and personal names.

Dr. E. B. Krumbhaar, of the University of Pennsylvania and the Editor of the Clio Series, has translated the short history of French Medicine by Drs. Laignel-Lavastine and Raymond Molinery. The book falls into the ordinary historical di-

visions, beginning with the period of curative magic and the Gallo-Roman Period. Chapter 3 discusses the real beginnings of French medicine, with an important section on the hospitals of the day, such as the Hotel Dieu of Paris. In the next chapter, which is extremely interesting, we are told how medicine was taught in France a thousand years ago and we learn about the various medical faculties, their powers and important functions. The chapter on the Renaissance is adequate, although comparatively little space is given to Paracelsus or his influence on the French medicine of the day. Chapter 9, dealing with the nineteenth century, is naturally so overloaded with material that it seems somewhat dull—a mere succession of names and discoveries. More interesting is the chapter on Military, Naval and Colonial Medicine. Of course, French medicine no longer holds the important place that it held in former times, such as in the eighteenth and early nineteenth centuries, when all intellectual Europe spoke French.

At the end of the book, there is an adequate index and the book is illustrated by fourteen portraits.

J. R. O.

Psychology and Health. By H. BANISTER, M.Sc., Ph.D. 256 pages; 13.5 × 20.5 cm. Macmillan Co., New York. 1935. Price, $2.50.

The author attempts a survey of psychology in some of its relations to health. "The difficulties which arise at various stages of development; (from infancy onwards) those which occur in physical health and those which follow physical sickness, have been considered, and the diverse kinds of psychological maladjustments which may result have been discussed. The views of the leaders of various schools of psycho-pathology have been outlined, and finally methods of treatment which have stood the test of experience have been sketched," in 245 small pages.

The book is very readable, if one wishes a superficial presentation of current psychological views. Hypnosis, little used, at least in this country, seems over stressed. The followers of the schools indicated (Freud, Jung and Adler) would probably take issue with this interpretation of their views. The genetic-dynamic formulation so widely followed in America is not mentioned. The chapters on treatment are well done, though even here the tendency to reduce everything to *a*, *b*, *c*, but rarely *d* rouses in us the profound wish—long since lost—that mental disease were this simple and easy to understand and treat.

H. M. M.

Food for the Diabetic. By MARY P. HUDDLESON. xvii + 110 pages; 13 × 19 cm. Macmillan Company, New York. 1934. Price, $1.50.

It is evident that this book has filled a demand because it is now in its third edition. The title is not quite accurate, since almost half the book is devoted to an exposition of the nature of diabetes and its medical treatment, to urinary examination, the administration of insulin and the prevention of the disease. The discussion of food measurement, the calculation of the food prescription, and the construction of meals are all clearly and logically developed. Two hundred grams of milk are considered an adequate adult intake (page 16); cereals and breads are to be selected from the "whole grain" variety. The food tables are well grouped, in nine small pages. They may be used both for weighed and measured diets. There is a chapter of recipes. The merit of this book lies in its simplicity and in its wise selection of essentials.

G. A. H.

Sex-Hygiene. What to Teach and How to Teach It. By ALFRED WORCESTER, M.D. 134 pages; 16 × 24 cm. Charles C. Thomas, Baltimore. 1934. Price, $2.50.

We have often wondered why it seems to be impossible to adopt the same objective, matter-of-fact attitude toward sex-hygiene and related topics that we show toward other forms of hygiene and medicine in general. Authors apparently must cloud the issue with moral and religious considerations, or titillate their readers with all the lurid details. This book is of the former type. It contains twelve pleasant, semi-religious essays which have been delivered over the course of the last thirty-five years to a variety of lay and professional groups of men and women. In Dr. Worcester's hands this may work well, but we are perfectly sure that if we responded to a question as to how far "petting parties" may go and what we thought of them by talking of our responsibility "to our Creator for the safeguarding of the human life life-stream"; by telling the boy he should treat the girl as he would wish his sister to be treated; by telling the girl she must win his respect and admiration and be true to his trust; and by telling both that "Restraint for each other's sake is in itself soul-satisfying and also a far more powerful motive than mere self-protection"; we would meet an incredulously lifted eye brow and politely restrained mirth.

Dr. Worcester's fundamental attitude is sound, but his exposition is not helpful in dealing with average young people, who do not seem to stop to think about their Creator very often or to make Him part of their daily lives.

H. M. M.

Diseases of Children. By SIR A. E. GARROD, FREDERICK E. BATTEN, HUGH THURSFIELD, and DONALD PATERSON. 1152 pages; 17 × 24.5 cm. William Wood and Company, Baltimore. 1934. Price, $10.00.

This is a new and completely revised edition of one of the leading English textbooks on pediatrics. The last edition was in 1929. The present volume shows many changes and additions.

The addition of an article on Heredity at the beginning of the book is a happy thought. The article on the teeth with stress laid on their maldevelopments and on their relation to general health is also a valuable feature. There are excellent discussions by Cameron on functional diseases of the nervous system and by Bray on allergy. The article by Sheldon on "Rheumatism" is admirably handled. In general the various contributors have maintained a high standard.

The American physician will not derive much value from certain statements on therapy because of unfamiliarity with the trade names of the Infant Formulary. He will be surprised also to learn that in pneumonia "the application of leeches over the hepatic area followed by hot fomentation to encourage further bleeding, will usually produce relief for the embarrassed right heart." (Page 432.) On page 47 viosterol dosage is stated as "a few drops given three times daily."

The rarer diseases are included and one finds space allotted to Von Gierke's disease, Progeria Alkaptonuria, etc. There is of necessity a certain amount of overlapping. Ample reference lists are handily placed at the end of each article. The illustrations are excellent and well selected; there are two valuable colored plates. The book as a whole is an excellent general pediatric text.

E. B.

COLLEGE NEWS NOTES

At the Annual Business Meeting of the College held at Philadelphia, May 2, 1935, the following elections took place.

A. Elective Officers:

President-Elect ..... Dr. Ernest B. Bradley, Lexington, Ky.
First Vice-President ..... Dr. Arthur R. Elliott, Chicago, Ill.
Second Vice-President ..... Dr. David P. Barr, St. Louis, Mo.
Third Vice-President ..... Dr. Egerton L. Crispin, Los Angeles, Calif.

B. Regents, term expiring 1938:

Dr. Jonathan C. Meakins ..... Montreal, Que.
Dr. James H. Means ..... Boston, Mass.
Dr. James B. Herrick ..... Chicago, Ill.
Dr. Charles G. Jennings ..... Detroit, Mich.
Dr. James E. Paullin ..... Atlanta, Ga.

C. Governors, term expiring 1938:

Dr. James F. Churchill ..... Southern California—San Diego
Dr. Gerald B. Webb ..... Colorado—Colorado Springs
Dr. Henry F. Stoll ..... Connecticut—Hartford
Dr. Wallace M. Yater ..... District of Columbia—Washington
Dr. Ernest E. Laubaugh ..... Idaho—Boise
Dr. Samuel E. Munson ..... Southern Illinois—Springfield
Dr. Robert M. Moore ..... Indiana—Indianapolis
Dr. Thomas Tallman Holt ..... Kansas—Wichita
Dr. William B. Breed ..... Massachusetts—Boston
Dr. Adolph Sachs ..... Nebraska—Omaha
Dr. Allen A. Jones ..... Western New York—Buffalo
Dr. Leander A. Riely ..... Oklahoma—Oklahoma City
Dr. Edward J. G. Beardsley ..... Eastern Pennsylvania—Philadelphia
Dr. E. Bosworth McCready ..... Western Pennsylvania—Pittsburgh
Dr. J. Owsley Manier ..... Tennessee—Nashville
Dr. Louis E. Viko ..... Utah—Salt Lake City
Dr. Jabez H. Elliott ..... Ontario—Toronto, Canada
Dr. William M. James ..... Panama and the Canal Zone

Term Expiring 1937:

Dr. C. W. Dowden ..... Kentucky—Louisville
Dr. C. G. Giddings ..... Georgia—Atlanta
Dr. Ramon M. Suarez ..... Puerto Rico—San Juan

At a meeting of the Board of Regents at Philadelphia, April 28, 1935, the following elections to Fellowship and Associateship were made.

Elected to Fellowship

April 28, 1935

Alexander, Archibald Addison ..... Oakland, Calif.
Alexander, Harry L. ..... St. Louis, Mo.
Baldwin, Louis B. ..... Tucson, Ariz.
Ball, Ralph G. ..... Manhattan, Kan.
Belk, William Parks ..... Ardmore, Pa.
Bell, J. Kenner ..... Detroit, Mich.
Black, James Harvey ..... Dallas, Texas
Boman, Paul Gerhard ..... Duluth, Minn.

Brown, Lewis Woodbridge.....Newark, N. J.
Burlingame, Clarence Charles.....Hartford, Conn.
Cardle, Archibald Evans.....Minneapolis, Minn.
Carns, Marie Louise.....Madison, Wis.
Chappell, Sidney L.....M. C., U. S. Army
Chrisman, William Walter.....Macon, Ga.
Colomb, Henry O.....Sykesville, Md.
Compton, Marion Lee.....Lexington, Ky.
Condry, Raphael Joseph.....Elkins, W. Va.
Corr, Wm. Philip.....Riverside, Calif.
Cottrell, James Ewing.....Philadelphia, Pa.
Cozby, Harold Otis.....M. C., U. S. Navy
Cronwell, Bernhard J., Jr.....Austin, Minn.
Crowe, Aldrich Clements.....Ocean City, N. J.
Deegan, John Kenneth.....Albany, N. Y.
Denison, Robert.....Harrisburg, Pa.
Denno, Willard Joseph.....New York, N. Y.
Dieuaide, Francis Raymond.....Peiping, China
Dillon, Edward Saunders.....Philadelphia, Pa.
Dollard, Henry Louis.....Washington, D. C.
Duhigg, Thomas F.....M. C., U. S. Navy
Durgin, Lawrence Newton.....Amherst, Mass.
Fenby, John S.....Baltimore, Md.
Fineman, Abraham Harold.....New York, N. Y.
Flinn, Robert Stanley.....Phoenix, Ariz.
Frazier, Chester North.....Peiping, China
Fregeau, Aime Napoleon.....San Francisco, Calif.
Gardner, Walter P.....Hastings, Minn.
Goldstein, Eli.....New York, N. Y.
Gordon, Burgess Lee.....Philadelphia, Pa.
Gordon, Douglas Meharg.....Ponca City, Okla.
Graham, William Randolph.....Richmond, Va.
Griffin, Mark Alexander.....Biltmore, N. C.
Griffith, George Cupp.....Philadelphia, Pa.
Harvey, Andrew.....New York, N. Y.
Helwig, Ferdinand C.....Kansas City, Kan.
Higgins, John Mark.....Sayre, Pa.
Hill, Walter Herbert.....San Antonio, Texas
Hines, Laurence Edward.....Chicago, Ill.
Horger, Eugene Leroy.....Columbia, S. C.
Hovenden, Ontie.....McGill, Nevada
Hunter, Melville Wallace.....Monroe, La.
Hutton, James H.....Chicago, Ill.
Ilsley, Morrill Leonard.....Claremont, Calif.
LaMont, Charles A.....Canton, Ohio
Lawson, Herman Albert.....Providence, R. I.
Leak, Roy L.....Middletown, Conn.
Levin, Charles Morris.....Richmond Hill, N. Y.
Levitas, George Max.....Westwood, N. J.
Lewis, Paul John.....Yakima, Wash.
Margolis, Harry Maurice.....Pittsburgh, Pa.
Markel, Albert G.....Paterson, N. J.
McEnerney, Charles Harold.....Washington, D. C.
McNeill, Philip M.....Oklahoma City, Okla.

Mitchell, Louis Albert.....Newark, Ohio
Morris, Sarah I.....Philadelphia, Pa.
Nakada, James Robert.....St. Louis, Mo.
Osgood, Carroll Wilcox.....Wauwatosa, Wis.
Randolph, Howell Sheppard.....Phoenix, Ariz.
Redwood, Frank Harrell.....Norfolk, Va.
Rose, Edwin Jehu.....Washington, D. C.
Schiltz, Frances Helen.....Wichita, Kan.
Scholz, Samuel B.....Philadelphia, Pa.
Scott, James Ralph.....New York, N. Y.
Sexton, Daniel Leritz.....St. Louis, Mo.
Sheldon, Lawrence Burton.....Dallas, Texas
Sinnock, Hildegardè Catherine G.....Quincy, Ill.
Sprague, Charles Harry.....Bridgeport, Conn.
Squires, Willard Haywood.....New York, N. Y.
Swalm, William A.....Philadelphia, Pa.
Whalen, Neil James.....Detroit, Mich.
Williman, Frank Louis.....Washington, D. C.
Wyckoff, John.....New York, N. Y.
Ylvisaker, Lauritz S.....Newark, N. J.

Elected to Associateship

April 28, 1935

Algie, William H.....Clay Center, Kan.
Allen, Kenneth Dayton Allison.....Denver, Colo.
Bach, Theodore Franklin.....Philadelphia, Pa.
Bailey, Fuller B.....Salt Lake City, Utah
Baird, David W.....Portland, Ore.
Baird, John Adams.....Dayton, Ohio
Barber, Thomas Maxfield.....Charleston, W. Va.
Bauer, Louis Hopewell.....Hempstead, N. Y.
Bell, George Erick.....Wilson, N. C.
Bennett, Clarence Rhodes.....Eufaula, Ala.
Bixby, Edward Welles.....Wilkes-Barre, Pa.
Black, Everett O.....Binghamton, N. Y.
Bonner-Miller, Lila Morse.....Raleigh, N. C.
Brennan, Joseph Patrick.....Pendleton, Ore.
Brines, Osborne Allen.....Detroit, Mich.
Brust, Raymond W.....Philadelphia, Pa.
Buchanan, J. Arthur.....Brooklyn, N. Y.
Buck, Burdette Jay.....Hartford, Conn.
Cahall, Walter Lawrence.....Philadelphia, Pa.
Cake, Charles Powell.....Washington, D. C.
Carlson, Glenn DeVere.....Dallas, Tex.
Catchings, Charles Evans.....Woodville, Miss.
Chavarria, Antonio Pena.....San Jose, Costa Rica
Ching, Richard Edward.....Memphis, Tenn.
Collman, Xavier Kuehn.....Wilkes-Barre, Pa.
Collins, Leon Howard, Jr.....Philadelphia, Pa.
Comroe, Bernard Isaac.....Philadelphia, Pa.
Connelly, Richard Campbell.....Detroit, Mich.
Conwell, Daniel Vincent.....Halstead, Kan.

Corrigan, George Francis.....Wichita, Kan.
Corrigan, John Cosgrove.....Boston, Mass.
Covner, Albert Henry.....Lynn, Mass.
Crane, Langdon Teachout.....Detroit, Mich.
Crellin, Jacob Antrim.....Lansdowne, Pa.
Danglade, James H.....Kansas City, Mo.
Daniels, Harry Anthony.....Oklahoma City, Okla.
Decherd, George Michael, Jr.....Galveston, Tex.
Deweese, Everett R.....Kansas City, Mo.
DuBois, Earl Danford.....Portland, Ore.
Durkin, Harry Anthony.....Peoria, Illinois
Egloff, William Chauncey.....Mason City, Iowa
Fetter, Ferdinand.....Philadelphia, Pa.
Flowers, Hiland L.....New York, N. Y.
Fortney, Arthur Conwell.....Fargo, N. D.
Foster, Robert Francis.....Rochester, Minn.
Foster, Stuart Oliver.....Washington, D. C.
Fox, Everett Clarence.....Dallas, Tex.
Gallison, Davis Thayer.....Boston, Mass.
Ganim, Joseph Nicholas.....Cincinnati, Ohio
Gillick, David W.....Shawnee, Okla.
Gilman, Ralph Lawrence.....Storrs, Conn.
Golan, Harry G.....Richmond Hill, N. Y.
Goldburgh, Harold L.....Philadelphia, Pa.
Gordon, Abraham S.....Brooklyn, N. Y.
Gordon, Harold.....Louisville, Ky.
Griffith, Reynold Stephen.....Philadelphia, Pa.
Hailey, David Walter.....Nashville, Tenn.
Hawkes, Richard Sylvester.....Portland, Maine
Hilton, John Palmer.....Denver, Colo.
Hindman, Samuel.....Cleveland, Ohio
Hitzrot, Lewis Haler.....Philadelphia, Pa.
Hoedemaker, Edward David.....Seattle, Wash.
Hoffman, Kelse Monjar.....Franklin, Pa.
Hood, Frederick Redding.....Oklahoma City, Okla.
Horan, Thomas M.....Detroit, Mich.
Horn, Benjamin.....Bridgeport, Conn.
Hufford, Clarence Elton.....Toledo, Ohio
Hunter, Charles Teague.....Newtown, Pa.
Ianne, Charles L.....San Jose, Calif.
Jantzen, George Howard.....Queens Village, N. Y.
Kennedy, Allan Souter.....Hamilton, Ont., Canada
Kennedy, Paul Augustin.....Englewood, N. J.
Keyes, Baldwin Longstreth.....Philadelphia, Pa.
Knight, Albert P.....Sayre, Pa.
Knighton, James Edward, Jr.....Shreveport, La.
Kullman, Harold John.....Detroit, Mich.
Landay, Louis Harold.....Aliquippa, Pa.
Lang, Samuel John.....Evanston, Illinois
LeBauer, Sidney F.....Greensboro, N. C.
Leonard, Noble Day.....North Chicago, Illinois
Lincoln, Cicero Lee.....Denver, Colo.

Lockie, L. Maxwell.....Buffalo, N. Y.
Maloney, Edward S.....Omaha, Nebr.
Margason, Merl L.....Portland, Ore.
Marlow, Arthur Ashley.....Peiping, China
Marr, Norval Mason.....St. Petersburg, Fla.
Martin, Maynard Waite.....Cleveland, Ohio
Masten, Alfred Roe.....Wheat Ridge, Colo.
McClenahan, William Urie.....Philadelphia, Pa.
McGee, Lemuel C.....Elkins, W. Va.
McGuire, Johnson.....Cincinnati, Ohio
McInerney, Michael J.....Washington, D. C.
McKay, Donald Robert.....Buffalo, N. Y.
Miller, James Roscoe.....Chicago, Illinois
Miller, Merle Middour.....Philadelphia, Pa.
Miller, William Lindsay.....Gadsden, Ala.
Moench, L. Mary.....New York, N. Y.
Molitch, Matthew.....Jamesburg, N. J.
Monte, Louis Anthony.....New Orleans, La.
Moore, Norman Slawson.....Ithaca, N. Y.
Moser, Rollin Henry.....Indianapolis, Ind.
Mudgett, William Chase.....Southern Pines, N. C.
Myers, Walter Kendall.....Washington, D. C.
Nye, Robert Bruce.....Philadelphia, Pa.
Osterman, Arthur Lee.....Wheeling, W. Va.
Perkin, Frank S.....Detroit, Mich.
Pitts, Thomas Antley.....Columbia, S. C.
Plotz, Milton.....Brooklyn, N. Y.
Plunkett, John Elmer.....Rochester, Minn.
Polansky, John Basil.....Glenside, Pa.
Potts, William Henry, Jr.....Dallas, Texas
Price, Alvin Edwin.....Detroit, Mich.
Pruit, Lee Tinkle.....Beaumont, Texas
Reddick, Walter Grady.....Dallas, Texas
Reed, Ivor Ellsworth.....Detroit, Mich.
Reichert, Philip.....New York, N. Y.
Rice, Raymond Maine.....Council Bluffs, Iowa
Robertson, Harold F.....Philadelphia, Pa.
Rosenfeld, Joseph.....Youngstown, Ohio
Rothenberg, Robert Charles.....Cincinnati, Ohio
Rubnitz, Abraham S.....Omaha, Nebr.
Sanders, Charles B.....Dallas, Texas
Schmitz, Henry L.....Chicago, Illinois
Schneck, Robert J.....Detroit, Mich.
Schoch, Arthur Gerhard.....Dallas, Texas
Scott, Ernest G.....Lynchburg, Va.
Selling, Lowell Sinn.....Detroit, Mich.
Sewell, Harry Dickey.....Huron, S. D.
Shapiro, Matthew.....New York, N. Y.
Simon, Frank A.....Louisville, Ky.
Smith, Euclid Monroe.....Hot Springs National Park, Ark.
Smith, Lauren Howe.....Philadelphia, Pa.
Smith, Percy King.....Wichita Falls, Texas

Smith, Richard Mays.....Dallas, Texas
Southcombe, Robert Henry.....Medical Lake, Wash.
Speight, Harold E.....Middletown, Conn.
Sprenkel, Vaughan Le Roy.....Allentown, Pa.
Stalker, Hugh.....Grosse Pointe, Mich.
Stiles, Merritt Henry.....Philadelphia, Pa.
Tolleson, Henry Madison.....Eastman, Ga.
Underwood, George R.....Lincoln, Nebr.
Walker, Thomas Tipton.....Watertown, N. Y.
Warvel, John Henry.....Indianapolis, Ind.
Wells, Robert Lomax.....Washington, D. C.
Whiting, Walter Belknap.....Wichita Falls, Texas
Willhelmy, Ellis W.....Kansas City, Mo.
Wilson, George Campbell.....Wallingford, Conn.
Wilson, Robert, Jr.....Charleston, S. C.
Wolfson, Mast.....Monterey, Calif.
Wood, Francis Clark.....Philadelphia, Pa.
Wood, J. K. Williams.....Willow Grove, Pa.

OBITUARY

WILLIAM SESSIONS HANNAH

Dr. William Sessions Hannah of Montgomery, Alabama, died of a streptococcus infection in Buffalo, New York, on March 22, 1935, after an illness of only a few days.

Dr. Hannah became an Associate of the College of Physicians in 1932 and was to be presented for Fellowship this year.

He was born in Pensacola, Florida, but had lived in Montgomery, Alabama, for many years. His academic education was obtained at the University of Alabama and Tulane University and he graduated in medicine at Johns Hopkins University in 1924. For four years he was an intern in the Union Memorial Hospital, finishing his internship in 1928, after which he located in his home town of Montgomery for the practice of his profession.

Dr. Hannah was a young man of splendid attainments. He was well trained medically, was a man of culture, and a gentleman of the highest type. He was rapidly making his mark in his profession and was destined to reach great heights. He had the respect and confidence of the community not only for his medical skill, but for his honor and integrity as a man. His death at so young an age is greatly to be deplored.

FRED WILKERSON, M.D., F.A.C.P.,
Governor for Alabama

DETROIT SELECTED FOR 1936 ANNUAL SESSION

At a meeting of the Board of Regents held May 3, 1935, on the closing day of the Philadelphia Annual Session, the invitation from Detroit for the 1936 Annual Session of the College was accepted by the Board of Regents. Dr. James Alex. Miller, President, appointed Dr. Charles G. Jennings of Detroit as General Chairman of the Session. Announcement will later be made of the hotel headquarters and the place of meetings.

The University of Michigan Medical School, located at Ann Arbor, will cooperate in the program for 1936.

The College last met in Detroit during 1926, at which time the American Congress on Internal Medicine was merged with the College, members of that Society becoming Associates of the College.

THE AMERICAN COLLEGE OF PHYSICIANS

Executive Secretary's Report on Operation 1934

The auditor's report of his examination of the accounts of the College is hereto attached. The statements disclose a further improvement over the preceding two years, as shown by the following:

1932 Surplus	$ 10,598.08
1933 "	5,801.06
1934 "	16,160.07

The 1934 surplus was distributed as follows:

Endowment Fund	$ 1,710.00
General Fund	14,450.07
	$ 16,160.07

The total principal of the two Funds on December 31, 1934, was

Endowment Fund	$ 55,720.00
General Fund	84,427.10
	$140,147.10

The larger surplus may be attributed to somewhat improved conditions among physicians, to additions to the membership, increased circulation of the Annals of Internal Medicine and a gradual transition from the smaller number of elections to Fellowship because of the "Associate first" rule which became operative in 1931. The number eligible for Fellowship was small during 1931, 1932 and 1933, but beginning 1934 the number began to increase, showing an appreciable effect on the income from initiation fees. The cost of printing the Annals of Internal Medicine was materially reduced during 1934 due to a change in printers.

Liquidating dividends were received from two of the former College depositories, now in the hands of receivers, in the total amount of $2,728.15, leaving a balance in such banks of $9,171.85.

A condensed comparison of income and expenditures for 1933 and 1934 appears on the following page.

The Executive Office has been conducted conservatively, with expenditures held to a minimum for effective operation.

Respectfully submitted,

(Signed) E. R. Loveland,
Executive Secretary.

April 28, 1935.

A Condensed Comparison of Income and Expenditures for 1933 and 1934

General Fund

Income:	1933	1934
Annual Dues	$20,069.80	$20,875.35
Initiation Fees	2,856.68	6,142.32
Interest on Investments	1,977.32	3,117.89
Interest on Bank Balances	243.28	22.50

Profit on Sale of Securities	2.96	1,178.39
Subscriptions, ANNALS OF INTERNAL MEDICINE	17,785.81	19,528.05
Advertising, ANNALS OF INTERNAL MEDICINE	4,540.20	4,455.28
Exhibits, Annual Clinical Session	4,192.21	6,124.85
Guest Fees, Annual Clinical Session	374.50	448.00
Miscellaneous Income	266.15	67.38
	$52,308.91	$61,960.01
Expenditures:		
Annual Clinical Session	$10,527.26	$11,646.40
ANNALS OF INTERNAL MEDICINE	19,540.36	19,216.05
Executive Secretary's Office	16,419.02	15,647.70
Miscellaneous	556.21	624.79
	$47,042.85	$47,134.94

Endowment Fund

Income:		
Interest on Investments	$ 2,385.86	$ 2,311.63
Life Membership Fees	635.00	1,710.00
	$ 3,020.86	$ 4,021.63
Expenditures:		
John Phillips' Memorial Award	$ 1,025.20	
Research Fellowship		$ 450.00

H. I. MACLEAN

Penarth Avenue and State Road

Bywood, Pa.

February 25, 1935

To the Board of Regents
American College of Physicians, Inc.
Philadelphia, Pa.

Mr. E. R. Loveland, Executive Secretary

Dear Sirs:

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ended December 31, 1934, and the accompanying statements, including the Balance Sheet at December 31, 1934, the analyses of the General Fund and the Endowment Fund, and the Statement of Operations for the year ended December 31, 1934, are in accordance with books of account and in my opinion set forth correctly the financial position at December 31, 1934, and the results of operations for the calendar year ended December 31, 1934, subject to the following comments:

Cash: The cash was properly accounted for. The following is a statement of the cash in the various depositories:

Girard Trust Company, Philadelphia	$37,020.57
Provident Trust Company, Philadelphia	17,239.44
Royal Bank of Canada, Montreal	3,933.82
Philadelphia Saving Fund Society (Time Deposit)	2,511.25
Western Saving Fund Society (Time Deposit)	2,511.25
	$63,216.33

The amount of cash in closed banks at January 1, 1934, was $11,900.00; during the year liquidating dividends amounting to $2,728.15 were received, which reduced the amount to $9,171.85, as shown by the following schedule.

	Balance Jan. 1, 1934	Liquidating Dividends	Balance Dec. 31, 1934
Bank of Pittsburgh, Pittsburgh	$ 5,847.87	$2,436.61	$3,411.26
Exchange National Bank, Pittsburgh ..	2,040.74	291.54	1,749.20
Highland National Bank, Pittsburgh ...	4,011.39	.....	4,011.39
	$11,900.00	$2,728.15	$9,171.85

Accounts Receivable: The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were properly accounted for by direct correspondence with the Girard Trust Company of Philadelphia, and the income for the year therefrom was verified. It was noted that the recommendation contained in the audit report that the securities be allocated to specific funds had not been carried out during the year ended December 31, 1934. However, it was further noted that the Board of Regents had taken action at the meeting of December 16, 1934, indicating that such allocation should be made. It is my understanding, after consultation with the Executive Secretary, Mr. E. R. Loveland, that the securities would be allocated to specific funds as of January 1, 1935. The net gain on the securities sold during this year has been credited to operations. The income from investments was distributed to the General Fund and to the Endowment Fund on the basis of the average yield for the period of 4.28 per cent. At December 31, 1934, the following security was in default:

	Interest in Default	
$2,000 City of Detroit, Mich., Lighting, 4¼, 1944	May, 1933	$42.50
	Nov., 1933	14.17 *
	May, 1934	14.17 *
	Nov., 1934	42.50

General: The increase in the amount of the Endowment Fund and the General Fund during the year 1934 is as follows:

	Balance Dec. 31, 1933	Balance Dec. 31, 1934	Net Increase
Endowment Fund	$ 54,010.00	$ 55,720.00	$ 1,710.00
General Fund	69,977.03	84,427.10	14,450.07
	$123,987.03	$140,147.10	$16,160.07

The accrued and deferred items have been recorded properly and were verified; the footings and extensions of the inventory were verified; the charges to the furniture and equipment accounts were proper and the allowance for depreciation appears to be adequate and all ascertainable liabilities have been included in the Balance Sheet. All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements as indicated by the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Very truly yours,

(Signed) H. I. MacLean,
Certified Public Accountant

* Part payments of the interest due on November 15, 1933, and May 15, 1934, were received amounting to $28.33 on each due date, or a total of $56.66.

AMERICAN COLLEGE OF PHYSICIANS, INC.

BALANCE SHEET, DECEMBER 31, 1934

Assets

Cash:			
In Banks and on Hand		$63,416.33	
In Closed Banks:			
Bank of Pittsburgh	$3,411.26		
Exchange National Bank, Pittsburgh	1,749.20		
Highland National Bank, Pittsburgh	4,011.39	9,171.85	$ 72,588.18
Accounts Receivable			303.35
Investments at cost, as annexed			64,986.06
Accrued Interest on Investments			726.77
Inventory of Keys, Pledges and Frames, at cost			332.69
Deferred Expenses, 19th Annual Clinical Session			2,146.49
Furniture and Equipment, at cost		$ 4,019.90	
Less, Allowance for Depreciation		2,348.59	1,671.31
			$142,754.85

Liabilities

Deferred Income:		
Advance Collections for Exhibits, Nineteenth Annual Clinical Session	$ 2,310.46	
Advance Subscriptions for Volume IX, ANNALS OF INTERNAL MEDICINE	297.29	2,607.75

Funds

Endowment Fund, as annexed	$55,720.00	
General Fund, as annexed	84,427.10	140,147.10
		$142,754.85

General Fund

For the Year Ended December 31, 1934

Balance, January 1, 1934		$69,977.03
Less:		
Transfer to Endowment Fund of the Initiation Fees of six new Life Members		375.00
		$69,602.03

Summary of Operations for the year ended December 31, 1934:

Income:		
Annual Dues	$20,875.35	
Subscriptions, ANNALS OF INTERNAL MEDICINE	19,528.05	
Advertising, ANNALS OF INTERNAL MEDICINE	4,455.28	
Initiation Fees	6,142.32	
Income from Invested Funds	3,117.89	
Profit on Sale of Securities	1,178.39	
Exhibits, 18th Annual Clinical Session	6,124.85	
Guest Fees, 18th Annual Clinical Session	448.00	
Other Income	89.88	$61,960.01
Expenses:		
Salaries	$17,415.60	
Postage, Telephone, Telegraph, etc.	2,571.87	
Office Supplies and Stationery	1,016.48	
Printing	14,269.52	
Rent and Maintenance	2,785.73	
Traveling Expenses	5,331.04	

Other Expenses:			
18th Annual Clinical Session	2,187.77		
Annals of Internal Medicine	349.66		
Executive Secretary's Office	602.48		
Miscellaneous	604.79	$47,134.94	
Net Income for the year ended December 31, 1934			14,825.07
Balance, December 31, 1934			$84,427.10

Endowment Fund

For the Year Ended December 31, 1934

Principal Account:		
Balance, January 1, 1934		$54,010.00
Add:		
Life Membership Fees received during 1934		1,335.00
Transfer of Initiation Fees of six new Life Members from General Fund		375.00
Total, December 31, 1934		$55,720.00
Income Account:		
Income from Securities (Endowment Fund only)		2,311.63
Less:		
Research Fellowship		450.00
Balance, Transferred to Operations for the Period		$ 1,861.63

Statement of Operations

For the Year Ended December 31, 1934

General Income:			
Annual Dues		$20,875.35	
Initiation Fees		6,142.32	
Income from Endowment Fund (Net, after deducting Research Fellowship stipend)		1,861.63	
Income from General Investments		1,256.26	
Profit on Sales of Securities (Net)		1,178.39	
Profit from Sale of Keys, Pledges and Frames		61.88	
Interest on Bank Balances		22.50	
Sales of 1933 Directory		5.50	$31,403.83
Eighteenth Annual Clinical Session:			
Income:			
Exhibits (Net)	$ 6,124.85		
Guest Fees	448.00	$ 6,572.85	
Expenses:			
Salaries	3,898.35		
Communications (Postage, Telephone, Etc.)	364.99		
Office Supplies and Stationery	68.12		
Printing	1,266.88		
Traveling Expenses	3,860.29		
Miscellaneous:			
Advertising	$ 159.65		
Badges	231.86		
Convocation and President's Reception	246.96		
Equipment Rental (Lanterns, etc.)	215.00		
Ladies Committee	165.37		
Publicity and Reporting	454.02		
Smoker	520.09		
Loss on Banquet (Net)	51.07		
Other Miscellaneous Items	143.75	$ 2,187.77	$11,646.40
Net Expenses of Clinical Session			$ 5,073.55

ANNALS OF INTERNAL MEDICINE:

Income:			
Subscriptions:			
Volume I	$ 6.90		
" II	7.90		
" III	7.30		
" IV	9.30		
" V	7.30		
" VI	50.37		
" VII	1,100.78		
" VIII	18,338.20	$19,528.05	
Advertising (Net)			
Volume VII	2,494.90		
" VIII	1,960.38	$ 4,455.28	
		23,983.33	
Expenses:			
Salaries	5,137.26		
Communications (Postage, Telephone, etc.)	842.23		
Office Supplies and Stationery	494.47		
Printing	12,392.43		
Miscellaneous	134.11		
Allowances, Adjustments and Purchases	215.55	$19,216.05	
Net Profit on ANNALS OF INTERNAL MEDICINE			4,767.28
Total Income			$36,171.11

Executive Secretary's Office:

Expenses:			
Salaries	$ 8,379.99		
Communications (Postage, Telephone, etc.)	1,364.65		
Office Supplies and Stationery	453.89		
Printing	610.21		
Rent and Maintenance	2,785.73		
Traveling Expenses	1,470.75		
Fee to Custodian of Securities	115.79		
Loss on Foreign Exchange	7.33		
Tax on Checks	13.83		
Loss on Sale of Equipment	15.20		
Miscellaneous	430.33	15,647.70	
ANNALS OF INTERNAL MEDICINE			
Distributed Free to Life Members		216.00	
Depreciation on Furniture and Equipment		408.79	21,346.04
Net Income for the Year Ended December 31, 1934			$14,825.07

INVESTMENTS

December 31, 1934

Par Value	Bonds	Cost
$ 2,000	Canadian National (West Indies) SS. Co., Ltd., 5s, 1955	$ 2,040.00
2,000	City and County of San Francisco, Calif., Fire Protection, 5s, 1941	2,137.12
2,000	City of Detroit, Mich., Lighting, 4¼s, 1944	2,010.40
2,000	City of Detroit, Mich., Street Railway, 4¼s, 1949	2,025.26
2,000	City of Houston, Tex., School District, 4¾s, 1942	2,077.50
1,000	City of Montreal, Canada, 5s, 1956	1,071.30
2,000	City of Toronto, Canada, Local Improvement, Debenture, 5s, 1936	2,020.00
5,000	Commonwealth Edison Co., First, Series "F," 4s, 1981	4,744.35
5,000	Government of the Dominion of Canada, 4s, 1960	4,662.50

5,000	New York and West Chester, Lighting, General Mortgage, 4s, 2004	5,044.35
5,000	Pennsylvania Railroad, General Mortgage, Series "E," 4¼s, 1984	5,013.10
2,000	Port of New York Authority, Interstate Bridge, Series "B," 4½s, 1952	2,042.20
2,000	Port of New York Authority, Interstate Tunnel, Series "E," 4¼s, 1958	2,065.40
1,000	Province of Ontario, Canada, Debenture, 5s, 1942	1,052.26
2,000	Province of Ontario, Canada, 4½s, 1942	2,015.00
3,000	U. S. Fourth Liberty Loan, 4¼s, 1938	3,079.69
2,000	U. S. Treasury, 4s, 1944–1954	1,998.13
20,000	U. S. Treasury, 4¼–3¼s, 1945	19,887.50
$65,000		$64,986.06

Circulation of Annals of Internal Medicine

In compliance with the regulations of the Code Authority for the Periodical Publishing and Printing Industry (A–3), the American College of Physicians, publishers of the Annals of Internal Medicine, presents the following statement concerning the circulation of said journal for the period beginning July 1934, and ending December 1934:

Average gross circulation	3,229
Average net paid circulation	3,101

Subscribed and sworn to by E. R. Loveland, Executive Secretary of the American College of Physicians, this fifteenth day of March, 1935.

My commission expires January 24, 1937.

(seal)

George E. Nitzsche,
Notary Public